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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America  
NEWS 2 "Ask CAS" for self-help around the clock  
NEWS 3 FEB 28 PATDPAFULL - New display fields provide for legal status  
data from INPADOc  
NEWS 4 FEB 28 BABS - Current-awareness alerts (SDIs) available  
NEWS 5 MAR 02 GBFULL: New full-text patent database on STN  
NEWS 6 MAR 03 REGISTRY/ZREGISTRY - Sequence annotations enhanced  
NEWS 7 MAR 03 MEDLINE file segment of TOXCENTER reloaded  
NEWS 8 MAR 22 KOREAPAT now updated monthly; patent information enhanced  
NEWS 9 MAR 22 Original IDE display format returns to REGISTRY/ZREGISTRY  
NEWS 10 MAR 22 PATDPASPC - New patent database available  
NEWS 11 MAR 22 REGISTRY/ZREGISTRY enhanced with experimental property tags  
NEWS 12 APR 04 EPFULL enhanced with additional patent information and new  
fields  
NEWS 13 APR 04 EMBASE - Database reloaded and enhanced  
NEWS 14 APR 18 New CAS Information Use Policies available online  
NEWS 15 APR 25 Patent searching, including current-awareness alerts (SDIs),  
based on application date in CA/CaPlus and USPATFULL/USPAT2  
may be affected by a change in filing date for U.S.  
applications.  
NEWS 16 APR 28 Improved searching of U.S. Patent Classifications for  
U.S. patent records in CA/CaPlus  
NEWS 17 MAY 23 GBFULL enhanced with patent drawing images  
NEWS 18 MAY 23 REGISTRY has been enhanced with source information from  
CHEMCATS  
NEWS 19 JUN 06 The Analysis Edition of STN Express with Discover!  
(Version 8.0 for Windows) now available  
NEWS 20 JUN 13 RUSSIAPAT: New full-text patent database on STN  
NEWS 21 JUN 13 FRFULL enhanced with patent drawing images  
NEWS 22 JUN 27 MARPAT displays enhanced with expanded G-group definitions  
and text labels  
NEWS 23 JUL 01 MEDICONF removed from STN  
NEWS 24 JUL 07 STN Patent Forums to be held in July 2005  
NEWS 25 JUL 13 SCISEARCH reloaded  
NEWS 26 JUL 20 Powerful new interactive analysis and visualization software,  
STN AnaVist, now available  
NEWS 27 AUG 11 Derwent World Patents Index(R) web-based training during  
August  
NEWS 28 AUG 11 STN AnaVist workshops to be held in North America  
  
NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT  
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005  
  
NEWS HOURS STN Operating Hours Plus Help Desk Availability  
NEWS INTER General Internet Information  
NEWS LOGIN Welcome Banner and News Items  
NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005

=> file registry  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

DICTIONARY FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> E "PEG"/CN 25

E1	1	PEFURAZOATE/CN
E2	1	PEFURAZOATE-IKI 220 MIXT./CN
E3	1 -->	PEG/CN
E4	1	PEG (POLYGLYCOL)/CN
E5	1	PEG 100/CN
E6	1	PEG 1000/CN
E7	1	PEG 1000 DIAMINE/CN
E8	1	PEG 1000 MONOSTEARATE/CN
E9	1	PEG 10000/CN
E10	1	PEG 1000MO/CN

E11	1	PEG 1000MS/CN
E12	1	PEG 100MS/CN
E13	1	PEG 11000/CN
E14	1	PEG 115/CN
E15	1	PEG 120 METHYL GLUCOSE DIOLEATE/CN
E16	1	PEG 120 METHYL GLUCOSE TRIOLEATE/CN
E17	1	PEG 12000/CN
E18	1	PEG 13000/CN
E19	1	PEG 1450/CN
E20	1	PEG 150 STEARATE/CN
E21	1	PEG 1500/CN
E22	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHALIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH DODECENYLSUCCINIC ANHYDRIDE/CN
E23	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHALIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH DODECENYLPHTHALIC ANHYDRIDE/CN
E24	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHALIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH PHTHALIC ANHYDRIDE/CN
E25	1	PEG 15000/CN

=> S E3

L1 1 PEG/CN

=> DIS L1 1 SQIDE

THE ESTIMATED COST FOR THIS REQUEST IS 6.15 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN

RN 25322-68-3 REGISTRY

CN Poly(oxy-1,2-ethanediyl),  $\alpha$ -hydro- $\omega$ -hydroxy- (9CI) (CA INDEX  
NAME)

OTHER NAMES:

CN	$\alpha,\omega$ -Hydroxypoly(ethylene oxide)
CN	$\alpha$ -Hydro- $\omega$ -hydroxypoly(oxy-1,2-ethanediyl)
CN	$\alpha$ -Hydro- $\omega$ -hydroxypoly(oxyethylene)
CN	1,2-Ethanediol, homopolymer
CN	16600
CN	1660S
CN	400DAB8
CN	Alkox
CN	Alkox E 100
CN	Alkox E 130
CN	Alkox E 160
CN	Alkox E 240
CN	Alkox E 30
CN	Alkox E 30G
CN	Alkox E 45
CN	Alkox E 60
CN	Alkox E 75
CN	Alkox R 100
CN	Alkox R 1000
CN	Alkox R 15
CN	Alkox R 150
CN	Alkox R 400
CN	Alkox SR
CN	Alkox SW
CN	Antarox E 4000
CN	Aquacide III
CN	Aquaffin
CN	Badimol
CN	BDH 301
CN	Bradsyn PEG
CN	Breox 2000
CN	Breox 20M
CN	Breox 4000
CN	Breox 550

CN Breox PEG 300  
CN CAFO 154  
CN Carbowax  
CN Carbowax 100  
CN Carbowax 1000  
CN Carbowax 1350  
CN Carbowax 14000  
CN Carbowax 1450  
CN Carbowax 1500  
CN Carbowax 1540  
CN Carbowax 20  
CN Carbowax 200  
CN Carbowax 20000  
CN Carbowax 25000  
CN Carbowax 300  
CN Carbowax 3350  
CN PEG

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for  
DISPLAY

AR 9002-90-8

DR 615575-04-7, 12676-74-3, 12770-93-3, 9081-95-2, 9085-02-3, 9085-03-4,  
174460-08-3, 174460-09-4, 54510-95-1, 125223-68-9, 54847-64-2, 59763-40-5,  
64441-68-5, 64640-28-4, 133573-31-6, 25104-58-9, 25609-81-8, 134919-43-0,  
101677-86-5, 99264-61-6, 106186-24-7, 112895-21-3, 114323-93-2,  
50809-04-6, 50809-59-1, 119219-06-6, 60894-12-4, 61840-14-0, 37361-15-2,  
112384-37-9, 67411-64-7, 70926-57-7, 75285-02-8, 75285-03-9, 77986-38-0,  
150872-82-5, 154394-38-4, 79964-26-4, 80341-53-3, 85399-22-0, 85945-29-5,  
90597-70-9, 88077-80-9, 88747-22-2, 34802-42-1, 107502-63-6, 107529-96-4,  
116549-90-7, 156948-19-5, 169046-53-1, 188364-77-4, 188924-03-0,  
189154-62-9, 191743-71-2, 196696-84-1, 201163-43-1, 206357-86-0,  
221638-71-7, 225502-44-3, 270910-26-4, 307928-07-0, 356055-70-4,  
391229-98-4

MF (C2 H4 O)n H2 O

CI PMS, COM

PCT Polyether

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,  
BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM\*,  
DIOGENES, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2,  
HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC,  
PDLCOM\*, PIRA, PROMT, RTECS\*, SCISEARCH, SPECINFO, TOXCENTER, TULSA,  
ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, TSCA\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent;  
Preprint; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);  
CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC  
(Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process);  
PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role  
in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical  
study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC  
(Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process);  
PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role  
in record)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
study); CMBI (Combinatorial study); FORM (Formation, nonpreparative);  
MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC  
(Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);  
NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical  
study); BIOL (Biological study); CMBI (Combinatorial study); FORM  
(Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence);

PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

/ Structure 1 in file .gra /

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

84039 REFERENCES IN FILE CA (1907 TO DATE)  
22615 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
84192 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
6.87	7.08

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

FILE LAST UPDATED: 20 AUG 2005 (20050820/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1

L2 185 L1

=> s PEG

9298 PEG

747 PEGS

L3 9685 PEG

(PEG OR PEGS)

=> s poly () ethylene () glycol

59257 POLY

6 POLIES

59263 POLY

(POLY OR POLIES)

18961 ETHYLENE

2287 ETHYLENES

19618 ETHYLENE

(ETHYLENE OR ETHYLENES)

22544 GLYCOL

27720 GLYCOLS

40275 GLYCOL

(GLYCOL OR GLYCOLS)

L4 2487 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol

66 METHOXYPOLY

18961 ETHYLENE  
 2287 ETHYLENES  
 19618 ETHYLENE  
       (ETHYLENE OR ETHYLENES)  
 22544 GLYCOL  
 27720 GLYCOLS  
 40275 GLYCOL  
       (GLYCOL OR GLYCOLS)  
 8421 ETHYLENE GLYCOL  
       (ETHYLENE(W) GLYCOL)  
 L5       52 METHOXYPOLY (W) ETHYLENE GLYCOL  
  
 => s 15 or 14 or 13  
 L6       10866 L5 OR L4 OR L3  
  
 => s antibod?  
 L7       694206 ANTIBOD?  
  
 => s clearance or clear or excret? or removed or removal  
       89107 CLEARANCE  
       5664 CLEARANCES  
       91341 CLEARANCE  
           (CLEARANCE OR CLEARANCES)  
       128624 CLEAR  
       549 CLEARS  
       129145 CLEAR  
           (CLEAR OR CLEARS)  
       116634 EXCRET?  
       99889 REMOVED  
       142890 REMOVAL  
       1080 REMOVALS  
       143364 REMOVAL  
           (REMOVAL OR REMOVALS)  
 L8       538410 CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
  
 => s 18 and 16  
 L9       1041 L8 AND L6  
  
 => s 19 and 17  
 L10      129 L9 AND L7  
  
 => s anti-PEG  
       574125 ANTI  
       6 ANTIS  
       574129 ANTI  
           (ANTI OR ANTIS)  
       9298 PEG  
       747 PEGS  
       9685 PEG  
           (PEG OR PEGS)  
 L11      7 ANTI-PEG  
           (ANTI(W) PEG)  
  
 => s l11 and 18  
 L12      2 L11 AND L8  
  
 => d ibib 1-2

L12 ANSWER 1 OF 2       MEDLINE on STN  
 ACCESSION NUMBER:   2002229521       MEDLINE  
 DOCUMENT NUMBER:   PubMed ID: 11966757  
 TITLE:           The in vivo effects of tumour necrosis factor blockade on  
                   the early cell mediated immune events and syndrome  
                   expression in rat adjuvant arthritis.  
 AUTHOR:           Bush K A; Kirkham B W; Walker J S

CORPORATE SOURCE: School of Physiology & Pharmacology, University of New South Wales, NSW, Australia.

SOURCE: Clinical and experimental immunology, (2002 Mar) 127 (3) 423-9.  
Journal code: 0057202. ISSN: 0009-9104.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200209

ENTRY DATE: Entered STN: 20020423  
Last Updated on STN: 20020906  
Entered Medline: 20020904

L12 ANSWER 2 OF 2 MEDLINE on STN

ACCESSION NUMBER: 2000191525 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10725103

TITLE: Efficient clearance of poly(ethylene glycol)-modified immunoenzyme with anti-PEG monoclonal antibody for prodrug cancer therapy.

AUTHOR: Cheng T L; Chen B M; Chern J W; Wu M F; Roffler S R

CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.

SOURCE: Bioconjugate chemistry, (2000 Mar-Apr) 11 (2) 258-66.  
Journal code: 9010319. ISSN: 1043-1802.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200005

ENTRY DATE: Entered STN: 20000613  
Last Updated on STN: 20000613  
Entered Medline: 20000531

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1

L3 9685 S PEG

L4 2487 S POLY () ETHYLENE () GLYCOL

L5 52 S METHOXPOLY () ETHYLENE GLYCOL

L6 10866 S L5 OR L4 OR L3

L7 694206 S ANTIBOD?

L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

L9 1041 S L8 AND L6

L10 129 S L9 AND L7

L11 7 S ANTI-PEG

L12 2 S L11 AND L8

=> s l11 not py>1999  
3085459 PY>1999

L13 3 L11 NOT PY>1999

=> d ibib 1-3

L13 ANSWER 1 OF 3 MEDLINE on STN

ACCESSION NUMBER: 1998089627 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9428158

TITLE: Immobilization of L-asparaginase into a biocompatible poly(ethylene glycol)-albumin hydrogel: evaluation of performance in vivo.  
AUTHOR: Jean-Francois J; D'Urso E M; Fortier G  
CORPORATE SOURCE: Departement de Chimie-Biochimie, Universite du Quebec, Montreal, Canada.  
SOURCE: Biotechnology and applied biochemistry, (1997 Dec) 26 ( Pt 3) 203-12.  
Journal code: 8609465. ISSN: 0885-4513.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199802  
ENTRY DATE: Entered STN: 19980217  
Last Updated on STN: 20000303  
Entered Medline: 19980205

L13 ANSWER 2 OF 3 MEDLINE on STN  
ACCESSION NUMBER: 84160696 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 6706424  
TITLE: Polyethylene glycol reactive antibodies in man: titer distribution in allergic patients treated with monomethoxy polyethylene glycol modified allergens or placebo, and in healthy blood donors.  
AUTHOR: Richter A W; Akerblom E  
SOURCE: International archives of allergy and applied immunology, (1984) 74 (1) 36-9.  
Journal code: 0404561. ISSN: 0020-5915.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198405  
ENTRY DATE: Entered STN: 19900319  
Last Updated on STN: 19970203  
Entered Medline: 19840522

L13 ANSWER 3 OF 3 MEDLINE on STN  
ACCESSION NUMBER: 83107741 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 6401699  
TITLE: Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol modified proteins.  
AUTHOR: Richter A W; Akerblom E  
SOURCE: International archives of allergy and applied immunology, (1983) 70 (2) 124-31.  
Journal code: 0404561. ISSN: 0020-5915.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198303  
ENTRY DATE: Entered STN: 19900318  
Last Updated on STN: 19900318  
Entered Medline: 19830311

=> d kwic 1

L13 ANSWER 1 OF 3 MEDLINE on STN  
AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, anti-PEG ) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of



fibroblast-like cell. . .

=> d kwic 2

L13 ANSWER 2 OF 3 MEDLINE on STN

AB . . . allergies and in healthy blood donors employing passive hemagglutination. In untreated allergic patients and in healthy blood donors, naturally occurring anti-PEG antibody titers between 32 and 512 were seen in 3.3 and 0.2%, respectively. During hyposensitization with monomethoxy polyethylene glycol modified ragweed extract and honey bee venom, respectively, the patients showed an anti-PEG antibody response. Titers of 32-512 were found in 50% of the patients directly after the first treatment course. After 2. . . years of treatment the percentage of patients with such titers declined to 28.5%. Mercaptoethanol treatment of sera indicated that the anti-PEG antibodies predominantly were of the IgM isotype. The weak IgM response found in treated patients is considered to be of. . .

=> d kwic 3

L13 ANSWER 3 OF 3 MEDLINE on STN

AB . . . protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an anti-PEG response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any anti-PEG antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA. . . mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate anti-PEG antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests.. . . by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7 -CH<sub>2</sub>CH<sub>2</sub>O-units. Anti-PEG antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance. . .

=> d ab 3

L13 ANSWER 3 OF 3 MEDLINE on STN

AB Antibodies to polyethylene glycol (PEG) were raised in rabbits by immunization with monomethoxy polyethylene glycol modified ovalbumin (OA), bovine superoxide dismutase (SOD), and ragweed pollen extract (Rag), given in Freund's complete adjuvant (FCA). Immunogenicity depended on the nature of the protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an anti-PEG response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any anti-PEG antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA was found nonimmunogenic in rabbits, and PEG of MW 5.9 X 10<sup>6</sup>, given s.c. to mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate anti-PEG antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests. PEG of MW greater than or equal to 4,000 produced specific precipitates, smaller molecules acted as monovalent haptens. From hapten inhibition of precipitation by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7 -CH<sub>2</sub>CH<sub>2</sub>O-units. Anti

-PEG antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance of these findings with regard to therapy with PEG-modified enzymes and allergens in humans remains to be established.

=> d kwic

L13 ANSWER 1 OF 3 MEDLINE on STN  
AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, anti-PEG ) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell. . .

=> d his

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FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999

=> s l10 not py>1999

3085459 PY>1999

L14 97 L10 NOT PY>1999

=> s l14 not py>1998

3546810 PY>1998

L15 90 L14 NOT PY>1998

=> s increase? or accelerat?

1841898 INCREASE?

88142 ACCELERAT?

L16 1898836 INCREASE? OR ACCELERAT?

=> s l16 and l15

L17 24 L16 AND L15

=> s l16 (S) 18

L18 51664 L16 (S) L8

=> s l18 and l17

L19 7 L18 AND L17

=> d ibib 1-4

L19 ANSWER 1 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 1998151177 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9492213

TITLE: Improved local delivery of TGF-beta2 by binding to injectable fibrillar collagen via difunctional polyethylene glycol.  
 AUTHOR: Bentz H; Schroeder J A; Estridge T D  
 CORPORATE SOURCE: Research and Development, Collagen Corporation, Palo Alto, California 94303, USA.  
 SOURCE: Journal of biomedical materials research, (1998 Mar 15) 39 (4) 539-48.  
 Journal code: 0112726. ISSN: 0021-9304.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199804  
 ENTRY DATE: Entered STN: 19980422  
 Last Updated on STN: 19980422  
 Entered Medline: 19980413

L19 ANSWER 2 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 97415461 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9271260  
 TITLE: Immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes.  
 AUTHOR: Harding J A; Engbers C M; Newman M S; Goldstein N I; Zalipsky S  
 CORPORATE SOURCE: SEQUUS Pharmaceuticals, Incorporated, Menlo Park, CA 94025, USA.  
 SOURCE: Biochimica et biophysica acta, (1997 Jul 25) 1327 (2) 181-92.  
 Journal code: 0217513. ISSN: 0006-3002.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199709  
 ENTRY DATE: Entered STN: 19970926  
 Last Updated on STN: 20000303  
 Entered Medline: 19970918

L19 ANSWER 3 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 95071855 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7981064  
 TITLE: The potential for enhanced tumour localisation by poly(ethylene glycol) modification of anti-CEA antibody.  
 AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A; Haines A M; King D J  
 CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, U.K.  
 SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30.  
 Journal code: 0370635. ISSN: 0007-0920.  
 PUB. COUNTRY: SCOTLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199501  
 ENTRY DATE: Entered STN: 19950116  
 Last Updated on STN: 19980206  
 Entered Medline: 19950103

L19 ANSWER 4 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 92235285 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1569204  
 TITLE: IgG antibody response to polyethylene

glycol-modified adenosine deaminase in patients with adenosine deaminase deficiency.

AUTHOR: Chaffee S; Mary A; Stiehm E R; Girault D; Fischer A; Hershfield M S

CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710.

CONTRACT NUMBER: DK20902 (NIDDK)

SOURCE: Journal of clinical investigation, (1992 May) 89 (5) 1643-51.  
Journal code: 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199205

ENTRY DATE: Entered STN: 19920612  
Last Updated on STN: 19920612  
Entered Medline: 19920526

=> d kwic 3

L19 ANSWER 3 OF 7 MEDLINE on STN

TI The potential for enhanced tumour localisation by poly(ethylene glycol) modification of anti-CEA antibody.

AB Attachment of poly(ethylene glycol) (PEG) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')<sub>2</sub> and Fab' fragments of the anti-CEA antibody A5B7 were chemically modified with PEG (M(r) 5,000), labelled with <sup>125</sup>I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. PEG modification of the intact antibody had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')<sub>2</sub> and Fab'A5B7 significantly prolonged plasma half-life and increased radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab'A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')<sub>2</sub> (M(r) 100,000), but after PEG attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact antibody. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after PEG attachment may therefore prove superior to either unmodified fragments or intact antibody for antibody-targeted therapy, although the increased plasma half-life may necessitate the use of a clearance mechanism.

CT Check Tags: In Vitro

\*Adenocarcinoma: IM, immunology

Animals

Antibodies, Monoclonal: CH, chemistry

\*Antibodies, Monoclonal: ME, metabolism

\*Carcinoembryonic Antigen: IM, immunology

\*Colonic Neoplasms: IM, immunology

Humans

Immunoglobulins, Fab: ME, metabolism

Mice

Mice, Nude

Neoplasm. . .

CN 0 (Antibodies, Monoclonal); 0 (Carcinoembryonic Antigen); 0 (Immunoglobulins, Fab); 0 (Polyethylene Glycols)

=> d kwic ibib 3

L19 ANSWER 3 OF 7 MEDLINE on STN

TI The potential for enhanced tumour localisation by poly(ethylene glycol) modification of anti-CEA antibody.

AB Attachment of poly(ethylene glycol) (PEG) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')<sub>2</sub> and Fab' fragments of the anti-CEA antibody A5B7 were chemically modified with PEG (M(r) 5,000), labelled with <sup>125</sup>I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. PEG modification of the intact antibody had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')<sub>2</sub> and Fab'A5B7 significantly prolonged plasma half-life and increased radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab'A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')<sub>2</sub> (M(r) 100,000), but after PEG attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact antibody. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after PEG attachment may therefore prove superior to either unmodified fragments or intact antibody for antibody-targeted therapy, although the increased plasma half-life may necessitate the use of a clearance mechanism.

CT Check Tags: In Vitro

\*Adenocarcinoma: IM, immunology  
Animals

Antibodies, Monoclonal: CH, chemistry

\*Antibodies, Monoclonal: ME, metabolism

\*Carcinoembryonic Antigen: IM, immunology

\*Colonic Neoplasms: IM, immunology

Humans

Immunoglobulins, Fab: ME, metabolism

Mice

Mice, Nude

Neoplasm. . .

CN 0 (Antibodies, Monoclonal); 0 (Carcinoembryonic Antigen); 0 (Immunoglobulins, Fab); 0 (Polyethylene Glycols)

ACCESSION NUMBER: 95071855 MEDLINE

DOCUMENT NUMBER: PubMed ID: 7981064

TITLE: The potential for enhanced tumour localisation by poly(ethylene glycol) modification of anti-CEA antibody.

AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A; Haines A M; King D J

CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, U.K.

SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30.  
Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199501

ENTRY DATE: Entered STN: 19950116  
Last Updated on STN: 19980206  
Entered Medline: 19950103

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

=> d ibib 5-7

L19 ANSWER 5 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 91334430 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1714590  
TITLE: Use of site-directed mutagenesis to enhance the  
epitope-shielding effect of covalent modification of  
proteins with polyethylene glycol.  
AUTHOR: Hershfield M S; Chaffee S; Koro-Johnson L; Mary A; Smith A  
A; Short S A  
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center,  
Durham, NC 27710.  
CONTRACT NUMBER: DK20902 (NIDDK)  
SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America, (1991 Aug 15) 88 (16) 7185-9.  
Journal code: 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-M60917; GENBANK-M66858; GENBANK-M66859;  
GENBANK-M66860; GENBANK-M66861; GENBANK-M66862;  
GENBANK-S45955; GENBANK-S45957; GENBANK-S45959;  
GENBANK-S49265  
ENTRY MONTH: 199109  
ENTRY DATE: Entered STN: 19911006  
Last Updated on STN: 19960129  
Entered Medline: 19910918

L19 ANSWER 6 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 89391643 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2789501  
TITLE: Low avidity antibodies to double stranded DNA in  
systemic lupus erythematosus: a longitudinal study of their  
clinical significance.  
AUTHOR: Nossent J C; Huysen V; Smeenk R J; Swaak A J

CORPORATE SOURCE: Department of Rheumatology, Dr Daniel den Hoed Clinic,  
Rotterdam, The Netherlands.  
SOURCE: Annals of the rheumatic diseases, (1989 Aug) 48 (8) 677-82.  
Journal code: 0372355. ISSN: 0003-4967.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198910  
ENTRY DATE: Entered STN: 19900309  
Last Updated on STN: 19900309  
Entered Medline: 19891020

L19 ANSWER 7 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 85003720 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 6479199  
TITLE: Association of circulating immune complexes with glomerular  
proteinuria in patients with transitional cell carcinoma of  
the urinary bladder.  
AUTHOR: Skaarup P; Jensenius J C; Brandslund I; Svehag S E; Wolf H  
SOURCE: European urology, (1984) 10 (4) 249-53.  
Journal code: 7512719. ISSN: 0302-2838.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198411  
ENTRY DATE: Entered STN: 19900320  
Last Updated on STN: 19900320  
Entered Medline: 19841101

=> d kwic 1

L19 ANSWER 1 OF 7 MEDLINE on STN  
AB To overcome rapid diffusion and clearance from the implant site  
and to increase stability, recombinant transforming growth  
factor beta2 (TGF-beta2) was covalently bound to injectable bovine dermal  
fibrillar collagen (FC) and its activity. . . to admixed TGF-beta2.  
Covalent binding was achieved in a two-step procedure: First, TGF-beta2  
was reacted with the difunctional polyethylene glycol (PEG)  
linker, and then the PEG-attached TGF-beta2 (PEG  
-TGF-beta2) was bound to the fibrillar collagen (FC-PEG  
-TGF-beta2). Initial binding of TGF-beta2 to difunctional succinimidyl  
glutarate (D-SG-PEG) or succinimidyl propionate polyethylene  
glycol (D-SE-PEG) linkers was completed after reacting for 8 or  
10 min as monitored by reverse-phase high-performance liquid  
chromatography. After reaction with injectable fibrillar collagen,  
extraction of unbound PEG-TGF-beta2 and Western blot analysis,  
using a TGF-beta specific antibody, demonstrated that at least  
85% of the TGF-beta2 was bound to the fibrillar collagen. The activity of  
PEG-TGF-beta2 was fully stable in phosphate-buffered saline at 4  
degrees C and 37 degrees C for at least up to 4. . . inactivated after  
1 week of incubation, as measured by the mink lung epithelial cell (Mv1Lu)  
growth inhibition assay. Formulations of FC-PEG-TGF-beta2  
containing 40 microg/ mL TGF-beta2 were implanted subcutaneously into rats  
and analyzed after days 7, 21, and 42. All TGF-beta2-containing. . .  
the TGF-beta typical fibroblastic response at the day 7 time point.  
Covalent binding of TGF-beta2 to collagen with both difunctional  
PEG crosslinkers resulted in a significantly stronger and  
longer-lasting TGF-beta2 response than that observed with admixed  
formulations of collagen and TGF-beta. The TGF-beta response with FC-  
PEG-TGF-beta2 lasted up to day 42 but was not seen after day 7 for  
TGF-beta2 admixed to FC. These findings clearly demonstrate that  
TGF-beta2 remains fully active after being covalently bound to collagen

via difunctional PEG. In addition, covalent binding potentiates and prolongs in vivo TGF-beta responses and stabilizes the TGF-beta in vitro. Results suggest that. . .

=> d kwic 2

L19 ANSWER 2 OF 7 MEDLINE on STN

TI Immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes.

AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, methoxypoly(ethylene glycol)-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-PEG-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized chimerized mouse IgG (C225, anti-human epidermal growth factor receptor) were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 ml/h). Subsequent injections of the immunoliposomes into the same animals resulted in rapid clearance (MRT < or = 0.7 h, Cl > or = 7 ml/h), which was accompanied by a significant increase in anti-C225 specific titers. Upon repeated injection or coinjection with the parent liposomes free C225 consistently exhibited prolonged circulation without any increase in C225-specific antisera, but, was cleared quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the preparations of PEG-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the antibody-mediated liposomal drug delivery effort.

CT Check Tags: Male  
Animals

Antibodies, Monoclonal: AD, administration & dosage

Antibodies, Monoclonal: IM, immunology

\*Drug Delivery Systems

Enzyme-Linked Immunosorbent Assay

Flow Cytometry

Humans

Immunoglobulins, Fab: ME, metabolism

\*Liposomes: IM, immunology

CN 0 (Antibodies, Monoclonal); 0 (Immunoglobulins, Fab); 0 (Liposomes); 0 (Phosphatidylethanolamines); 0 (Polyethylene Glycols); EC 2.7.1.112 (Receptor, Epidermal Growth Factor)

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

9.14

16.22

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 23 Aug 2005 VOL 143 ISS 9  
FILE LAST UPDATED: 22 Aug 2005 (20050822/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> s PEG

33003 PEG  
1125 PEGS  
L20 33476 PEG  
(PEG OR PEGS)

=> s poly () ethylene () glycol

644812 POLY  
2 POLIES  
644813 POLY  
(POLY OR POLIES)  
506522 ETHYLENE  
3337 ETHYLENES  
507988 ETHYLENE  
(ETHYLENE OR ETHYLENES)  
334892 GLYCOL  
44021 GLYCOLS  
349919 GLYCOL  
(GLYCOL OR GLYCOLS)  
L21 12996 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol

228 METHOXYPOLY  
506522 ETHYLENE  
3337 ETHYLENES  
507988 ETHYLENE  
(ETHYLENE OR ETHYLENES)  
334892 GLYCOL  
44021 GLYCOLS  
349919 GLYCOL  
(GLYCOL OR GLYCOLS)  
122310 ETHYLENE GLYCOL  
(ETHYLENE(W) GLYCOL)  
L22 144 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s 122 or 121 or 120

L23 41717 L22 OR L21 OR L20

=> s antibod?

L24 440322 ANTIBOD?

=> s clearance or clear or excret? or removed or removal

67750 CLEARANCE  
5064 CLEARANCES  
69883 CLEARANCE  
(CLEARANCE OR CLEARANCES)  
191308 CLEAR  
942 CLEARS  
192117 CLEAR  
(CLEAR OR CLEARS)  
158408 EXCRET?  
390380 REMOVED  
620820 REMOVAL  
5047 REMOVALS  
622011 REMOVAL  
(REMOVAL OR REMOVALS)

L25 1304988 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

=> s clearance or clear? or excret? or removed or removal

67750 CLEARANCE

5064 CLEARANCES

69883 CLEARANCE

(CLEARANCE OR CLEARANCES)

422339 CLEAR?

158408 EXCRET?

390380 REMOVED

620820 REMOVAL

5047 REMOVALS

622011 REMOVAL

(REMOVAL OR REMOVALS)

L26 1459976 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

=> s increase? or accelerat?

3483178 INCREASE?

330235 ACCELERAT?

L27 3736368 INCREASE? OR ACCELERAT?

75% OF LIMIT FOR TOTAL ANSWERS REACHED

=> s 126 (S) 127

L28 99738 L26 (S) L27

=> s 124 and 128

L29 1750 L24 AND L28

=> s 129 and 123

L30 16 L29 AND L23

=> s anti-PEG

378223 ANTI

9 ANTIS

378230 ANTI

(ANTI OR ANTIS)

33003 PEG

1125 PEGS

33476 PEG

(PEG OR PEGS)

L31 9 ANTI-PEG

(ANTI(W) PEG)

=> s 131 not py>1999

5788970 PY>1999

L32 3 L31 NOT PY>1999

=> d ibib 1-3

L32 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:239090 CAPLUS

DOCUMENT NUMBER: 131:63325

TITLE: Accelerated Clearance of Polyethylene Glycol-Modified Proteins by Anti-Polyethylene Glycol IgM

AUTHOR(S): Cheng, Tian-Lu; Wu, Pin-Yi; Wu, Ming-Fang; Chern, Ji-Wang; Roffler, Steve R.

CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

SOURCE: Bioconjugate Chemistry (1999), 10(3), 520-528

CODEN: BCCHEs; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN .  
 ACCESSION NUMBER: 1998:24552 CAPLUS  
 DOCUMENT NUMBER: 128:162592  
 TITLE: Immobilization of L-asparaginase into a biocompatible  
 poly(ethylene glycol)-albumin hydrogel: evaluation of  
 performance in vivo  
 AUTHOR(S): Jean-Francois, Jacques; D'urso, Edith Marie; Fortier,  
 Guy  
 CORPORATE SOURCE: Laboratoire d'Enzymologie Appliquee, Departement de  
 Chimie-Biochimie, Universite du Quebec, Montreal,  
 Montreal, QC, H3C 3P8, Can.  
 SOURCE: Biotechnology and Applied Biochemistry (1997), 26(3),  
 203-212  
 CODEN: BABIEC; ISSN: 0885-4513  
 PUBLISHER: Portland Press Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1983:15249 CAPLUS  
 DOCUMENT NUMBER: 98:15249  
 TITLE: Antibodies against polyethylene glycol produced in  
 animals by immunization with monomethoxy polyethylene  
 glycol-modified proteins  
 AUTHOR(S): Richter, Ary Wolfgang; Aakerblom, Eva  
 CORPORATE SOURCE: Dep. Biomed. Res., Pharm. AB, Uppsala, 75104, Swed.  
 SOURCE: International Archives of Allergy and Applied  
 Immunology (1983), 70(2), 124-31  
 CODEN: IAAAAM; ISSN: 0020-5915  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
 E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
 L3 9685 S PEG  
 L4 2487 S POLY () ETHYLENE () GLYCOL  
 L5 52 S METHOXPOLY () ETHYLENE GLYCOL  
 L6 10866 S L5 OR L4 OR L3  
 L7 694206 S ANTIBOD?  
 L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
 L9 1041 S L8 AND L6  
 L10 129 S L9 AND L7  
 L11 7 S ANTI-PEG  
 L12 2 S L11 AND L8  
 L13 3 S L11 NOT PY>1999  
 L14 97 S L10 NOT PY>1999  
 L15 90 S L14 NOT PY>1998  
 L16 1898836 S INCREASE? OR ACCELERAT?  
 L17 24 S L16 AND L15  
 L18 51664 S L16 (S) L8  
 L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
 L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
 L22 144 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
 L23 41717 S L22 OR L21 OR L20  
 L24 440322 S ANTIBOD?  
 L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
 L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
 L27 3736368 S INCREASE? OR ACCELERAT?  
 L28 99738 S L26 (S) L27  
 L29 1750 S L24 AND L28  
 L30 16 S L29 AND L23  
 L31 9 S ANTI-PEG  
 L32 3 S L31 NOT PY>1999

=> s l30 not py>1998

6611305 PY>1998

L33 6 L30 NOT PY>1998

=> d ibib 1-3

L33 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:90995 CAPLUS  
 DOCUMENT NUMBER: 128:196557  
 TITLE: Improved local delivery of TGF- $\beta$ 2 by binding to  
 injectable fibrillar collagen via difunctional  
 polyethylene glycol  
 AUTHOR(S): Bentz, H.; Schroeder, J. A.; Estridge, T. D.  
 CORPORATE SOURCE: Research and Development, Collagen Corporation, Palo  
 Alto, CA, 94303, USA  
 SOURCE: Journal of Biomedical Materials Research (1998),  
 39(4), 539-548  
 CODEN: JBMRBG; ISSN: 0021-9304  
 PUBLISHER: John Wiley & Sons, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:463486 CAPLUS  
 DOCUMENT NUMBER: 127:99686  
 TITLE: Immunogenicity-pharmacokinetics relationship of  
 polyethylene glycol-grafted immunoliposomes  
 AUTHOR(S): Zalipsky, S.; Harding, J. A.; Engbers, C. M.; Newman,  
 M. S.; Goldstein, N. I.  
 CORPORATE SOURCE: SEQUUS Pharmaceuticals, Inc., Menlo Park, CA, 94025,  
 USA  
 SOURCE: Proceedings of the International Symposium on  
 Controlled Release of Bioactive Materials (1997),  
 24th, 87-88  
 CODEN: PCRMEY; ISSN: 1022-0178  
 PUBLISHER: Controlled Release Society, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:420003 CAPLUS  
 DOCUMENT NUMBER: 127:140290  
 TITLE: Immunogenicity and pharmacokinetic attributes of  
 poly(ethylene glycol  
 )-grafted immunoliposomes  
 AUTHOR(S): Harding, Jennifer A.; Engbers, Charles M.; Newman,  
 Mary S.; Goldstein, Neil I.; Zalipsky, Samuel  
 CORPORATE SOURCE: SEQUUS Pharmaceuticals, Incorporated, 960 Hamilton  
 Court, Menlo Park, USA

SOURCE: Biochimica et Biophysica Acta (1997), 1327(2), 181-192  
 CODEN: BBACAQ; ISSN: 0006-3002  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic 2

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
 AB Preps. of site-specifically constructed, aggregation free PEG  
 -grafted immunoliposomes are more immunogenic than free C225  
 antibodies (Ab). This immunogenicity potentiation was almost  
 entirely due to the constant human Fc region of the Ab. Presence of  
 C225-specific Ab's in the immunoliposome-treated rats dramatically  
 accelerated clearance of subsequently injected  
 immunoliposomes or free C225. Negligible response to the Fab portion of  
 conjugated C225 was detected, suggesting that use of Fab' as a targeting  
 moiety on PEG-liposomes is less likely to cause immunogenicity  
 related problems. These observations are of importance to  
 antibody-mediated liposomal drug delivery.  
 ST immunoliposome PEG grafted antibody  
 IT Epidermal growth factor receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (antibodies to; immunogenicity-pharmacokinetics relationship  
 of polyethylene glycol-grafted immunoliposomes)  
 IT Polyoxyalkylenes, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU  
 (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (derivs., conjugates with C225 antibody; immunogenicity-  
 pharmacokinetics relationship of polyethylene glycol-grafted  
 immunoliposomes)  
 IT Antibodies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU  
 (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (to EGF receptor, conjugates with PEG derivs.;  
 immunogenicity-pharmacokinetics relationship of polyethylene  
 glycol-grafted immunoliposomes)  
 IT 25322-68-3D, Peg, derivs., conjugates with C225 antibody  
 171115-99-4D, derivs., conjugates with C225 antibody  
 178744-28-0D, derivs., conjugates with C225 antibody  
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU  
 (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (immunogenicity-pharmacokinetics relationship of polyethylene  
 glycol-grafted immunoliposomes)

=> d kwic 3

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
 TI Immunogenicity and pharmacokinetic attributes of poly(  
 ethylene glycol)-grafted immunoliposomes  
 AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine,  
 cholesterol, methoxypoly(ethylene glycol  
 )-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-  
 PEG-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized  
 chimerized mouse IgG (C225, anti-human epidermal growth factor receptor)  
 were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 mL/h).  
 Subsequent injections of the immunoliposomes into the same animals  
 resulted in rapid clearance (MRT≤0.7 h, Cl≥7  
 mL/h), which was accompanied by a significant increase in  
 anti-C225 specific titers. Upon repeated injection or coinjection with  
 the parent liposomes free C225 consistently exhibited prolonged

circulation without any increase in C225-specific antisera, but was cleared quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of the immunoliposome induced antisera against human. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the preps. of PEG-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the antibody-mediated liposomal drug delivery effort.

- ST immunoliposome PEG grafted; pharmacokinetics immunoliposome PEG grafted
- IT Immunoglobulins  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(G; immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)
- IT Epidermal growth factor receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(antibodies to; immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)
- IT Phosphatidylcholines, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)
- IT Drug delivery systems  
(immunoliposomes; immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)
- IT Polyoxyalkylenes, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(reaction products with distearoylphosphatidylethanolamine, hydrazide derivative; immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)
- IT 4537-76-2DP, Distearoylphosphatidylethanolamine, reaction products with PEG derivs. 9004-74-4DP, Methoxypolyethylene glycol, reaction products with distearoylphosphatidylethanolamine 25322-68-3DP, PEG, reaction products with distearoylphosphatidylethanolamine, hydrazide derivative  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(immunogenicity and pharmacokinetic attributes of poly(ethylene glycol)-grafted immunoliposomes)

=> d ibib 4-6

L33 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:292108 CAPLUS

DOCUMENT NUMBER: 122:75593

TITLE: The potential for enhanced tumor localization by poly(ethylene glycol) modification of anti-CEA antibody

AUTHOR(S): Pedley, R. B.; Boden, J. A.; Boden, R.; Begent, R. H. J.; Turner, A.; Haines, A. M. R.; King, D. J.

CORPORATE SOURCE: Department Clinical Oncology, Royal Free Hospital School Medicine, London, NW3 2PF, UK

SOURCE: British Journal of Cancer (1994), 70(6), 1126-30  
CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal  
LANGUAGE: English

L33 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1993:250975 CAPLUS  
DOCUMENT NUMBER: 118:250975  
TITLE: Radioimmunoassay for the pyridinoline crosslinked  
carboxy-terminal telopeptide of type I collagen: a new  
serum marker of bone collagen degradation  
AUTHOR(S): Risteli, Juha; Elomaa, Inkeri; Niemi, Seija; Novamo,  
Anne; Risteli, Leila  
CORPORATE SOURCE: Dep. Med. Biochem., Univ. Oulu, Oulu, SF-90220,  
Finland  
SOURCE: Clinical Chemistry (Washington, DC, United States)  
(1993), 39(4), 635-40  
CODEN: CLCHAU; ISSN: 0009-9147  
DOCUMENT TYPE: Journal  
LANGUAGE: English

L33 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1991:550137 CAPLUS  
DOCUMENT NUMBER: 115:150137  
TITLE: Use of site-directed mutagenesis to enhance the  
epitope-shielding effect of covalent modification of  
proteins with polyethylene glycol  
AUTHOR(S): Hershfield, Michael S.; Chaffee, Sara; Koro-Johnson,  
Lillian; Mary, Ann; Smith, Albert A.; Short, Steven A.  
CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, 27710, USA  
SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America (1991), 88(16), 7185-9  
CODEN: PNASA6; ISSN: 0027-8424  
DOCUMENT TYPE: Journal  
LANGUAGE: English

=> file pctfull  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
62.60	78.82

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-1.46	-1.46

CA SUBSCRIBER PRICE

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005  
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FILE LAST UPDATED: 22 AUG 2005 <20050822/UP>  
MOST RECENT UPDATE WEEK: 200533 <200533/EW>  
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s PEG

33330 PEG  
4725 PEGS

L34 35377 PEG  
(PEG OR PEGS)

=> s poly () ethylene () glycol

106749 POLY  
281 POLIES  
107011 POLY

(POLY OR POLIES)  
94414 ETHYLENE

486 ETHYLENES  
 94496 ETHYLENE  
 (ETHYLENE OR ETHYLENES)  
 99346 GLYCOL  
 38678 GLYCOLS  
 106001 GLYCOL  
 (GLYCOL OR GLYCOLS)  
 L35 5321 POLY (W) ETHYLENE (W) GLYCOL  
  
 => s methoxypoly () ethylene glycol  
 179 METHOXYPOLY  
 94414 ETHYLENE  
 486 ETHYLENES  
 94496 ETHYLENE  
 (ETHYLENE OR ETHYLENES)  
 99346 GLYCOL  
 38678 GLYCOLS  
 106001 GLYCOL  
 (GLYCOL OR GLYCOLS)  
 34591 ETHYLENE GLYCOL  
 (ETHYLENE(W)GLYCOL)  
 L36 76 METHOXYPOLY (W) ETHYLENE GLYCOL  
  
 => s antibod?  
 L37 80487 ANTIBOD?  
  
 => s clearance or clear? or excret? or removed or removal  
 40394 CLEARANCE  
 3516 CLEARANCES  
 41825 CLEARANCE  
 (CLEARANCE OR CLEARANCES)  
 285091 CLEAR?  
 16591 EXCRET?  
 339076 REMOVED  
 14 REMOVEDS  
 339079 REMOVED  
 (REMOVED OR REMOVEDS)  
 186688 REMOVAL  
 807 REMOVALS  
 186876 REMOVAL  
 (REMOVAL OR REMOVALS)  
 L38 492783 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
  
 => s increase? or accelerat?  
 477801 INCREASE?  
 83290 ACCELERAT?  
 L39 496097 INCREASE? OR ACCELERAT?  
  
 => s 138 (S) 139  
 L40 83462 L38 (S) L39  
  
 => s anti-PEG  
 159836 ANTI  
 158 ANTIS  
 159865 ANTI  
 (ANTI OR ANTIS)  
 33330 PEG  
 4725 PEGS  
 35377 PEG  
 (PEG OR PEGS)  
 L41 7 ANTI-PEG  
 (ANTI(W) PEG)  
  
 => s 141 and 140  
 L42 5 L41 AND L40



=> d ibib 1-3

L42 ANSWER 1 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 2005072385 PCTFULL ED 20050816 EW 200532  
TITLE (ENGLISH): PITUITARY ADENYLATE CYCLASE ACTIVATING PEPTIDE (PACAP)  
RECEPTOR (VPAC2) AGONISTS AND THEIR PHARMACOLOGICAL  
METHODS OF USE  
TITLE (FRENCH): AGONISTES DU RECEPTEUR (VPAC2) DU TYPE PEPTIDES  
ACTIVANT L'ADENYLATE CYCLASE HYPOPHYSIAIRE (PACAP) ET  
PROCEDES PHARMACOLOGIQUES D'UTILISATION DE CES  
AGONISTES  
INVENTOR(S): CLAIRMONT, Kevin, 80 Merwin Circle, Cheshire,  
Connecticut 06410, US [US, US];  
LUMB, Kevin, J., 520 Granite Road, Guilford,  
Connecticut 06437, US [US, US];  
BUCKHOLZ, Thomas, 10 Morehouse Avenue, Milford,  
Connecticut 06460, US [US, US];  
SALHANICK, Arthur, I., 430 Bellevue Road, New Haven,  
Connecticut 06511, US [US, US]  
PATENT ASSIGNEE(S): BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane,  
West Haven, Connecticut 06516, US [US, US], for all  
designates States except US;  
CLAIRMONT, Kevin, 80 Merwin Circle, Cheshire,  
Connecticut 06410, US [US, US], for US only;  
LUMB, Kevin, J., 520 Granite Road, Guilford,  
Connecticut 06437, US [US, US], for US only;  
BUCKHOLZ, Thomas, 10 Morehouse Avenue, Milford,  
Connecticut 06460, US [US, US], for US only;  
SALHANICK, Arthur, I., 430 Bellevue Road, New Haven,  
Connecticut 06511, US [US, US], for US only  
AGENT: GREENMAN, Jeffrey, M.\$, Bayer Pharmaceuticals  
Corporation, 400 Morgan Lane, West Haven, Connecticut  
06516\$, US  
LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005072385	A2	20050811

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO):

BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT  
LT LU MC NL PL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2005-US2609 A 20050127

PRIORITY INFO.:

US 2004-60/539,550 20040127

US 2004-60/566,499 20040429

L42 ANSWER 2 OF 5

PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 2005016974 PCTFULL ED 20050302 EW 200508  
TITLE (ENGLISH): SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND  
CONJUGATION  
TITLE (FRENCH): DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET  
A LA CONJUGAISON PROTEINIQUE  
INVENTOR(S): JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
Hamilton House, Mabledon Place, London WC1H 9BB, GB

[IN, GB];  
 LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [GB, GB];  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [CA, GB];  
 HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies  
 Limited, Suite 303, Hamilton House, Mabledon Place,  
 London WC1H 9BB, GB [GB, GB];  
 PAPAANNOU, Yiannis, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [GR, GB]

PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton  
 House, Mabledon Place, London WC1H 9BB, GB [GB, GB],  
 for all designates States except US;  
 JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [IN, GB], for US only;  
 LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [GB, GB], for US only;  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [CA, GB], for US only;  
 HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies  
 Limited, Suite 303, Hamilton House, Mabledon Place,  
 London WC1H 9BB, GB [GB, GB], for US only;  
 PAPAANNOU, Yiannis, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon  
 Street, London EC2M 7LH\$, GB

LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
 CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
 HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
 MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
 RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
 VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW  
 RW (EAPO): AM AZ BY KG KZ MD RU TJ TM  
 RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
 MC NL PL PT RO SE SI SK TR  
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-GB3511 A 20040812  
 PRIORITY INFO.: EP 2003-03254989.1 20030812

L42 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 2005016973 PCTFULL ED 20050302 EW 200508  
 TITLE (ENGLISH): POLYSIALIC ACID DERIVATIVES  
 TITLE (FRENCH): DERIVES D'ACIDE POLYSIALIQUE  
 INVENTOR(S): HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies  
 Limited, Suite 303, Hamilton House, Mabledon Place,  
 London WC1H 9BB, GB [GB, GB];  
 JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [IN, GB];

LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [GB, GB];  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [CA, GB];  
 PAPAIOANNOU, Iaonnis, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [GR, GB]  
 PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton  
 House, Mabledon Place, London WC1H 9BB, GB [GB, GB],  
 for all designates States except US;  
 HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies  
 Limited, Suite 303, Hamilton House, Mabledon Place,  
 London WC1H 9BB, GB [GB, GB], for US only;  
 JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [IN, GB], for US only;  
 LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
 Hamilton House, Mabledon Place, London WC1H 9BB, GB  
 [GB, GB], for US only;  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [CA, GB], for US only;  
 PAPAIOANNOU, Iaonnis, Lipoxen Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [GR, GB], for US only  
 AGENT: GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon  
 Street, London EC2M 7LH\$, GB  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	-----		
	WO 2005016973	A1	20050224
DESIGNATED STATES			
W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW		
RW (ARIPO):	BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW		
RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM		
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR		
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2004-GB3488	A	20040812
PRIORITY INFO.:	EP 2003-03254988.3		20030812
	EP 2003-03255200.2		20030821

=> d ibib 4-5

L42 ANSWER 4 OF 5  
 ACCESSION NUMBER: 2004030617 PCTFULL ED 20040421 EW 200416  
 TITLE (ENGLISH): POLYMER CONJUGATES WITH DECREASED ANTIGENICITY,  
 METHODS OF PREPARATION AND USES THEREOF  
 TITLE (FRENCH): CONJUGUES DE POLYMERES AVEC ANTIGENICITE REDUITE,  
 PROCEDES DE PREPARATION ET UTILISATIONS DE CES  
 CONJUGUES  
 INVENTOR(S): MARTINEZ, Alexa, L., 1944 Jonathan Avenue, San Jose, CA  
 95125, US;  
 SHERMAN, Merry, R., 1114 Royal Lane, San Carlos, CA

94070, US;  
 SAIFER, Mark, G., P., 1114 Royal Lane, San Carlos, CA  
 94070, US;  
 WILLIAMS, L. David, 37709 Arlene Court, Fremont, CA  
 94536, US  
 PATENT ASSIGNEE(S): MOUNTAIN VIEW PHARMACEUTICALS, INC., 3475-S Edison Way,  
 Menlo Park, CA 94025, US [US, US]  
 AGENT: GOLDSTEIN, Jorge A.\$, Sterne, Kessler, Goldstein & Fox,  
 P.L.L.C., 1100 New York Avenue, N.W., Washington, DC  
 20005\$, US  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004030617	A2	20040415

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR  
 CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU  
 ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA  
 MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC  
 SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU  
 ZA ZM ZW

RW (ARIPO):

GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
 MC NL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2003-US29989 A 20030925

PRIORITY INFO.:

US 2002-60/414,424 20020930

US 2002-10/317,092 20021212

L42 ANSWER 5 OF 5

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2005 Univentio on STN

TITLE (ENGLISH):

2001015726 PCTFULL ED 20020828

TITLE (FRENCH):

COMPOSITIONS FOR STIMULATING CYTOKINE SECRETION AND  
 INDUCING AN IMMUNE RESPONSE

INVENTOR(S):

COMPOSITIONS STIMULANT LA SECRETION DE CYTOKINE ET  
 PROVOQUANT UNE REACTION IMMUNITAIRE

SEMPLE, Sean, C.;  
 HARASYM, Troy, O.;  
 KLIMUK, Sandra, K.;  
 KOJIC, Ljiljiana, D.;  
 BRAMSON, Jonathan, L.;  
 MUI, Barbara;  
 HOPE, Michael, J.

PATENT ASSIGNEE(S):

INEX PHARMACEUTICALS CORP.;  
 SEMPLER, Sean, C.;  
 HARASYM, Troy, O.;  
 KLIMUK, Sandra, K.;  
 KOJIC, Ljiljiana, D.;  
 BRAMSON, Jonathan, L.;  
 MUI, Barbara;  
 HOPE, Michael, J.

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001015726	A2	20010308

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU  
 CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN  
 IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK  
 MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
 TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD

	SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
	DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG
	CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:	WO 2000-CA1013                      A    20000828
PRIORITY INFO.:	US 1999-60/151,211                      19990827
	US 2000-60/176,406                      20000113

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
E "PEG"/CN 25

L1                      1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2                      185 S L1  
L3                      9685 S PEG  
L4                      2487 S POLY () ETHYLENE () GLYCOL  
L5                      52 S METHOXYPOLY () ETHYLENE GLYCOL  
L6                      10866 S L5 OR L4 OR L3  
L7                      694206 S ANTIBOD?  
L8                      538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9                      1041 S L8 AND L6  
L10                      129 S L9 AND L7  
L11                      7 S ANTI-PEG  
L12                      2 S L11 AND L8  
L13                      3 S L11 NOT PY>1999  
L14                      97 S L10 NOT PY>1999  
L15                      90 S L14 NOT PY>1998  
L16                      1898836 S INCREASE? OR ACCELERAT?  
L17                      24 S L16 AND L15  
L18                      51664 S L16 (S) L8  
L19                      7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20                      33476 S PEG  
L21                      12996 S POLY () ETHYLENE () GLYCOL  
L22                      144 S METHOXYPOLY () ETHYLENE GLYCOL  
L23                      41717 S L22 OR L21 OR L20  
L24                      440322 S ANTIBOD?  
L25                      1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26                      1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27                      3736368 S INCREASE? OR ACCELERAT?  
L28                      99738 S L26 (S) L27  
L29                      1750 S L24 AND L28  
L30                      16 S L29 AND L23  
L31                      9 S ANTI-PEG  
L32                      3 S L31 NOT PY>1999  
L33                      6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34                      35377 S PEG  
L35                      5321 S POLY () ETHYLENE () GLYCOL  
L36                      76 S METHOXYPOLY () ETHYLENE GLYCOL  
L37                      80487 S ANTIBOD?  
L38                      492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39                      496097 S INCREASE? OR ACCELERAT?  
L40                      83462 S L38 (S) L39  
L41                      7 S ANTI-PEG  
L42                      5 S L41 AND L40

=> s 134 or 135 or 136

L43                      38102 L34 OR L35 OR L36

=> s 143 (S) 137  
L44 3934 L43 (S) L37

=> s 144 and 140  
L45 1413 L44 AND L40

=> s 144 (P) 140  
L46 1018 L44 (P) L40

=> s anti-(polyethylene glycol)  
MISSING OPERATOR 'ANTI-(POLYETHYLE'  
The search profile that was entered contains terms or  
nested terms that are not separated by a logical operator.

=> s anti () (polyethylene glycol)  
159836 ANTI  
158 ANTIS  
159865 ANTI  
(ANTI OR ANTIS)  
123593 POLYETHYLENE  
5298 POLYETHYLENES  
124334 POLYETHYLENE  
(POLYETHYLENE OR POLYETHYLENES)  
99346 GLYCOL  
38678 GLYCOLS  
106001 GLYCOL  
(GLYCOL OR GLYCOLS)  
62856 POLYETHYLENE GLYCOL  
(POLYETHYLENE(W)GLYCOL)  
L47 3 ANTI (W) (POLYETHYLENE GLYCOL)

=> d ibib 1-3

L47 ANSWER 1 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 2005016974 PCTFULL ED 20050302 EW 200508  
TITLE (ENGLISH): SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND  
CONJUGATION  
TITLE (FRENCH): DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET  
A LA CONJUGAISON PROTEINIQUE  
INVENTOR(S): JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
Hamilton House, Mabledon Place, London WC1H 9BB, GB  
[IN, GB];  
LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
Hamilton House, Mabledon Place, London WC1H 9BB, GB  
[GB, GB];  
GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
Suite 303, Hamilton House, Mabledon Place, London WC1H  
9BB, GB [CA, GB];  
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies  
Limited, Suite 303, Hamilton House, Mabledon Place,  
London WC1H 9BB, GB [GB, GB];  
PAPAOANNOU, Yiannis, Lipoxen Technologies Limited,  
Suite 303, Hamilton House, Mabledon Place, London WC1H  
9BB, GB [GR, GB]  
PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton  
House, Mabledon Place, London WC1H 9BB, GB [GB, GB],  
for all designates States except US;  
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
Hamilton House, Mabledon Place, London WC1H 9BB, GB  
[IN, GB], for US only;  
LAING, Peter, Lipoxen Technologies Limited, Suite 303,  
Hamilton House, Mabledon Place, London WC1H 9BB, GB  
[GB, GB], for US only;  
GREGORIADIS, Gregory, Lipoxen Technologies Limited,

Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;  
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only  
GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon Street, London EC2M 7LH\$, GB

AGENT:

LANGUAGE OF FILING:  
LANGUAGE OF PUBL.:  
DOCUMENT TYPE:  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO):

BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2004-GB3511 A 20040812

PRIORITY INFO.:

EP 2003-03254989.1 20030812

L47 ANSWER 2 OF 3

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

2005016973 PCTFULL ED 20050302 EW 200508

TITLE (ENGLISH):

POLYSIALIC ACID DERIVATIVES

TITLE (FRENCH):

DERIVES D'ACIDE POLYSIALIQUE

INVENTOR(S):

HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];  
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];  
PAPAIIOANNOU, Iannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB]  
LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;  
HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;  
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H

PATENT ASSIGNEE(S):

9BB, GB [CA, GB], for US only;  
 PAPAIOANNOU, Ioannis, Lipoxon Technologies Limited,  
 Suite 303, Hamilton House, Mabledon Place, London WC1H  
 9BB, GB [GR, GB], for US only.  
 AGENT: GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon  
 Street, London EC2M 7LH\$, GB  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016973	A1	20050224

# DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
 CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
 HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
 MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
 RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
 VC VN YU ZA ZM ZW  
 RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW  
 RW (EAPO): AM AZ BY KG KZ MD RU TJ TM  
 RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
 MC NL PL PT RO SE SI SK TR  
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG  
 APPLICATION INFO.: WO 2004-GB3488 A 20040812  
 PRIORITY INFO.: EP 2003-03254988.3 20030812  
 EP 2003-03255200.2 20030821

L47 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 2004022000 PCTFULL ED 20040324 EW 200412  
 TITLE (ENGLISH): ANTIBIOTIC MICROSPHERES FOR TREATMENT OF INFECTIONS AND  
 OSTEO MYELITIS  
 TITLE (FRENCH): MICROSPHERES ANTIBIOTIQUES POUR LE TRAITEMENT  
 D'INFECTIONS ET DE L'OSTEO MYELITE  
 INVENTOR(S): AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030,  
 US [US, US];  
 CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US  
 [US, US];  
 MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251,  
 US [US, US]  
 PATENT ASSIGNEE(S): AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030,  
 US [US, US];  
 CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US  
 [US, US];  
 MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251,  
 US [US, US]  
 AGENT: RODDY, Kenneth, A.\$, Suite 100, 2916 West T.C. Jester,  
 Houston, TX 77018\$, US  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004022000	A2	20040318

# DESIGNATED STATES

W: AE AG AL AU BA BB BR BZ CA CN CO CR CU DM DZ EC GD GE  
 HR ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX  
 NI NO NZ OM PG PH PL SC SG SY TN TT UA UZ VC VN YU ZA  
 GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
 RW (ARIPO): AM AZ BY KG KZ MD RU TJ TM  
 RW (EAPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
 RW (EPO): MC NL PT RO SE SI SK TR  
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG



APPLICATION INFO.: WO 2003-US28010 A 20030905  
PRIORITY INFO.: US 2002-60/408,496 20020905  
US 2002-60/408,502 20020905

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY () ETHYLENE () GLYCOL  
L5 52 S METHOXPOLY () ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY () ETHYLENE () GLYCOL  
L22 144 S METHOXPOLY () ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999  
L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
L35 5321 S POLY () ETHYLENE () GLYCOL  
L36 76 S METHOXPOLY () ETHYLENE GLYCOL  
L37 80487 S ANTIBOD?  
L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40  
L43 38102 S L34 OR L35 OR L36  
L44 3934 S L43 (S) L37  
L45 1413 S L44 AND L40  
L46 1018 S L44 (P) L40  
L47 3 S ANTI () (POLYETHYLENE GLYCOL)

=> s 146 not py>1999  
581472 PY>1999  
L48 282 L46 NOT PY>1999

=> s 143/ab  
662 PEG/AB  
227 PEGS/AB  
831 PEG/AB  
((PEG OR PEGS)/AB)  
3882 POLY/AB  
132 POLIES/AB  
4014 POLY/AB  
((POLY OR POLIES)/AB)  
6371 ETHYLENE/AB  
22 ETHYLENES/AB  
6377 ETHYLENE/AB  
((ETHYLENE OR ETHYLENES)/AB)  
3431 GLYCOL/AB  
453 GLYCOLS/AB  
3707 GLYCOL/AB  
((GLYCOL OR GLYCOLS)/AB)  
122 POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB  
0 METHOXYPOLY/AB  
6371 ETHYLENE/AB  
22 ETHYLENES/AB  
6377 ETHYLENE/AB  
((ETHYLENE OR ETHYLENES)/AB)  
3431 GLYCOL/AB  
453 GLYCOLS/AB  
3707 GLYCOL/AB  
((GLYCOL OR GLYCOLS)/AB)  
604 ETHYLENE GLYCOL/AB  
((ETHYLENE(W)GLYCOL)/AB)  
0 METHOXYPOLY/AB (W) ETHYLENE GLYCOL/AB  
L49 930 ((PEG/AB) OR (POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB) OR (METHOXY  
POLY/AB (W) ETHYLENE GLYCOL/AB))

=> s 149 and 148  
L50 12 L49 AND L48

=> s 150 not py>1998  
649032 PY>1998  
L51 11 L50 NOT PY>1998

=> d ibib 1-5

L51 ANSWER 1 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1998048837 PCTFULL ED 20020514  
TITLE (ENGLISH): POLYALKYLENE OXIDE-MODIFIED SINGLE CHAIN POLYPEPTIDES  
TITLE (FRENCH): POLYPEPTIDES A CHAINE UNIQUE MODIFIES PAR OXYDE DE  
POLYALKYLENE  
INVENTOR(S): WHITLOW, Marc;  
SHORR, Robert, G., L.;  
FILPULA, David, R.;  
LEE, Lihsyng, S.  
PATENT ASSIGNEE(S): ENZON, INC.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9848837	A1	19981105

DESIGNATED STATES

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC

	LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU
	SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM
	KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE
	CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ
	CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.:	WO 1998-US8654 A 19980430
PRIORITY INFO.:	US 1997-60/044,449 19970430
	US 1997-60/050,472 19970623
	US 1997-60/063,074 19971027
	US 1997-60/067,341 19971202

L51 ANSWER 2 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 1998044143 PCTFULL ED 20020514  
 TITLE (ENGLISH): POLYMER-MODIFIED VIRUSES  
 TITLE (FRENCH): VIRUS MODIFIES PAR DES POLYMERES  
 INVENTOR(S): SMITH, Alan, E.;

O'RIORDAN, Catherine, R.;

PATENT ASSIGNEE(S): FRANCIS, Gillian, E.;

PARKES, Vincent;

DELGADO, Christina

GENZYME CORPORATION;

POLYMASC PHARMACEUTICAL, PLC;

SMITH, Alan, E.;

O'RIORDAN, Catherine, R.;

FRANCIS, Gillian, E.;

PARKES, Vincent;

DELGADO, Christina

LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
-----		
WO 9844143	A1	19981008

DESIGNATED STATES  
 W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
 ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC  
 LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU  
 SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH  
 GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT  
 BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF  
 BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.:	WO 1998-US6609	A	19980403
PRIORITY INFO.:	GB 1997-9706735.9		19970403
	GB 1997-9719625.7		19970915
	GB 1997-9722316.8		19971022

L51 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 1997010847 PCTFULL ED 20020514  
 TITLE (ENGLISH): TARGETING OF CONJUGATES OF POLY(ETHYLENE GLYCOL) AND  
 ANTIBODIES AGAINST GLUTAMIC ACID DECARBOXYLASE TO ISLET  
 CELLS

TITLE (FRENCH): CIBLAGE DE CONJUGUES DE POLY(ETHYLENE GLYCOL) ET  
 D'ANTICORPS CONTRE L'ACIDE GLUTAMIQUE DECARBOXYLASE SUR  
 DES CELLULES INSULAIRES

INVENTOR(S): JACOBS, Harvey;

KIM, Sung, Wan;

MENARD, Virginie

PATENT ASSIGNEE(S): UNIVERSITY OF UTAH RESEARCH FOUNDATION

LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
-----		
WO 9710847	A1	19970327

DESIGNATED STATES

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT  
LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI  
SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY  
KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT  
LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD  
TG

APPLICATION INFO.: WO 1996-US15219 A 19960920  
PRIORITY INFO.: US 1995-60/004,109 19950921

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1997003092 PCTFULL ED 20020514  
TITLE (ENGLISH): A PROCESS FOR REMOVAL OF POLYETHYLENE GLYCOL FROM A  
PROTEIN OR PEPTIDE SOLUTION  
TITLE (FRENCH): PROCEDE POUR ELIMINER LE POLYETHYLENEGLYCOL D'UNE  
SOLUTION DE PROTEINES OU DE PEPTIDES  
INVENTOR(S): KAERSGAARD, Per;  
CARLSEN, Soren, Knud  
PATENT ASSIGNEE(S): HEMASURE A/S;  
KAERSGAARD, Per;  
CARLSEN, Soren, Knud  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9703092	A1	19970130

DESIGNATED STATES  
W: JP US AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT  
SE

APPLICATION INFO.: WO 1996-DK314 A 19960710  
PRIORITY INFO.: DK 1995-823/95 19950713  
DK 1995-970/95 19950904

L51 ANSWER 5 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1996034015 PCTFULL ED 20020514  
TITLE (ENGLISH): MODIFIED ANTI-ICAM-1 ANTIBODIES AND THEIR USE IN THE  
TREATMENT OF INFLAMMATION  
TITLE (FRENCH): ANTICORPS ANTI-ICAM-1 MODIFIES ET LEUR UTILISATION DANS  
LE TRAITEMENT DES INFLAMMATIONS  
INVENTOR(S): FAANES, Ronald, B.;  
MC GOFF, Paul, E.;  
SHIRLEY, Bret, A.;  
SCHER, David, S.  
PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;  
FAANES, Ronald, B.;  
MC GOFF, Paul, E.;  
SHIRLEY, Bret, A.;  
SCHER, David, S.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9634015	A1	19961031

DESIGNATED STATES  
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI  
GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR  
TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD  
RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL  
PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-US5550 A 19960423  
PRIORITY INFO.: US 1995-8/427,355 19950424

=> d kwic 4

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN Polyethylene is used for fractional precipitation of proteins and peptides. Protein and peptide fractions obtained by the PEG fractionation methods generally contains residual PEG. The invention relates to a process for removing contaminating PEG from a solution of proteins or peptides, which process comprises adsorption of PEG in the protein or peptide solution to activated carbon.

ABFR . . . fractionnaire des proteines et des peptides.  
Les fractions de proteines et de peptides obtenues selon les methodes de fractionnement par PEG contiennent generalement des residus de PEG. La presente invention concerne un procede permettant d'eliminer d'une solution de proteines ou de peptides le PEG contaminant, lequel procede consiste a adsorber le PEG contenu dans la solution sur un carbone active.

DETD . . . application having publication number 123,375 describes manufacturing of a dry  $\gamma$ -globulin preparation capable of intravenous injection by fractionating human plasma with PEG. The method provides a  $\gamma$ -globulin preparation with improved water solubility and stability against increase of anticomplementary activity and decrease of antibody titer.

In one aspect of this invention, the activated carbon is added to the PEG-containing protein or peptide solution batchwise, and after. . . PEG, the activated carbon is separated from the solution by methods known per se such as centrifugation, sedimentation, or filtration. The removed activated carbon may subsequently be washed and the washing solution may be added to the purified, more protein or peptide containing solution, to increase the recovery of, for example, a valuable protein or peptide in the purified solution.

. . . carbon filter with a flow rate that permits the adsorption of the PEG to the activated carbon in the filter. The removal of the PEG by filtration may be combined with the removal of other contaminating substances, with a decolorization, or with a clarification of the solution by the activated carbon filter. The filtration. . . may subsequently be washed and the washing solution may be added to the purified more protein or peptide containing solution, to increase the recovery of e.g. a valuable protein or peptide in the treated solution.

=> d kwic 3

L51 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN . . . coupled to a nonimmunogenic hydrophilic polymer that provides a hydration shell around the monoclonal antibody for inhibiting immune recognition thereof. Poly(ethylene glycol) is a preferred polymer. A method of reducing insulinitis in an IDDM patient and a composition

therefor are also described.

ABFR . . . non immunogene  
qui forme une enveloppe d'hydratation autour de l'anticorps monoclonal  
en vue d'inhiber la  
reconnaissance immune de celui-ci. Le poly(ethylene  
glycol) est un polymere prefere. L'invention se  
rapporte egalement a un procede de reduction de l'insulite chez un  
patient atteint d'IDDM, . . .

DETD TARGETING OF CONJUGATES OF POLY(ETHYLENE  
GLYCOL) AND ANTIBODIES AGAINST  
GLUTAMIC ACID DECARBOXYLASE TO ISLET CELLS 11  
CROSS-REFERENCE TO RELATED APPLICATIONS  
This application claims the benefit of U.S.

From an immunotherapeutic approach, overt early  
stage diabetes has been treated by blocking the  
activating receptors on T cells with monoclonal  
antibodies. In one such study, anti-lymphocyte serum  
(ALS) and antibodies directed against CD4 and Cd8 T cell  
receptors were administered to diabetic mice. T. Maki  
et al., Long-term Abrogation of Autoimmune Diabetes. . . within 30  
days after  
treatment and lasted for about 200 days. Several  
significant points about the autoimmunity of diabetes  
were observed. The lymphocytic antibodies were  
responsible for termination of the immune response,  
thereby allowing islet recovery. Also, if antibody  
BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS  
FIG. 1 shows the reactions for coupling methoxy-  
PEG-amine to an F(ab) fragment with a  
heterobifunctional crosslinker.

Preferably, the polymer is a poly (ethylene  
glycol) ,  
and more preferably has a molecular weight in the range  
of about 200 to 8,000, although higher molecular weight  
polymers, branched polymers, star molecules, and PEG  
block copolymers are also within the scope of the  
invention. Methoxy-PEG is a particularly preferred  
polymer. It is also preferred that the monoclonal  
antibody or fragment thereof is an F (ab I ) fragment.

In the present invention, anti-GAD monoclonal  
antibodies (Mab) are modified to maintain binding to  
their cognate antigens while further preventing  
recognition by other aspects of the immune system. In  
an illustrative embodiment, the anti-GAD antibody is  
modified by digestion with a protease and chemical  
reduction with a reducing agent to yield F(ab')  
fragments, which are then conjugated with various  
poly(ethylene glycol) polymers ( PEG). The F(ab')  
fragment retains the antigen-specific Fab binding  
fragment, while the immune and complement activating Fc  
fragment is removed. In addition, the poly(  
ethylene  
glycol) moiety provides an increased hydration  
sphere  
and dynamic mobility that prevents protein and cellular  
interaction. Thus, the present anti-GAD-F(ab')-PEG  
composition simultaneously binds GAD and prevents or  
inhibits further recognition by the immune system.

Antibodies administered to experimental animals and

hydrophilic surfaces, due to the hydrating effect of PEG. More importantly, protein (albumin and other plasma proteins) adsorption was greatly reduced, resulting from the high chain motility, hydration sphere, and protein exclusion properties of PEG.

pH 7.3) and then incubated in 250  $\mu$ l of blocking buffer for 1 hour at 37°C. After incubation, the blocking buffer was removed and the Immunol. 98-104 (1978), hereby incorporated by reference. To further increase the immune reactivity of the F(ab') fragment, poly(ethylene glycol) (PEG) is conjugated to the F(ab) molecule. PEG is a linear or branched, neutral.

ascites fluid was microplate was dried. Duplicate dilutions (50  $\mu$ l) of samples containing anti-GAD (IgG, F(ab'), or F(ab) -PEG) (serum or dilutions of chromatographic fractions) were placed in the wells and incubated for 2 hours at 37°C, followed by 3 washes with. . . microplate autoreader (EL311, is Bio-Tek Instruments). These values were compared to standard curves prepared with known anti-GAD concentrations to extrapolate the anti-GAD antibody concentration.

either Example 1 or Example 2 was enzymatically digested and then chemically reduced to obtain F(ab) fragments, which could then be coupled to PEG. The rationale behind this procedure is to obtain an antibody fragment capable of binding to the GAD antigen yet which lacks the Fc domain, and is conjugated with PEG to further decrease protein and cellular interactions.

It was anticipated that the antibodies isolated during the previous procedures were a mixture of anti-GAD and indigenous mouse antibodies. As a final antigenicity of foreign immunogenic proteins and enzymes. Therefore, PEGs of various molecular weights are coupled to the F(ab') fragments through the sulfhydryl groups thereof. These anti-GAD-F(ab')-PEG compositions maintain ability to bind to islet/beta cells while the PEG moiety masks the remainder of the F(ab') molecule from eliciting additional immunological events.

#### Example 8

##### Coupling of Anti-GAD-F(ab) to Activated PEG

In this example, a PEG intermediate prepared according to the procedure of Examples 4, 6, or 7 is Example 5

##### Activation of Diamino-PEG

For cell staining and whole body perfusion (pharmacokinetic) evaluations, it is useful to label anti-GAD-F(ab)-PEG with, for example, a radioactive or fluorescent label. In vivo therapeutic applications of the anti-GAD-F(ab)-PEG generally do not require such labels. Current methods of labeling antibodies involve forming conjugates through amine groups (fluorescent or  $^{125}$ I labels) or through oxidation of tyrosine residues (125, label). These labeling methods can interfere with antibody binding through reaction with the active site of the antibody. Therefore, this example shows coupling of the label to the PEG moiety. The labeled PEG

moiety  
is later coupled to the F (ab I ) fragment. This procedure  
assures that labeled and unlabeled compositions have  
similar affinities for. . .

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005 .

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
L22 144 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999  
L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
L35 5321 S POLY ( ) ETHYLENE ( ) GLYCOL  
L36 76 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
L37 80487 S ANTIBOD?  
L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40  
L43 38102 S L34 OR L35 OR L36  
L44 3934 S L43 (S) L37  
L45 1413 S L44 AND L40  
L46 1018 S L44 (P) L40  
L47 3 S ANTI ( ) (POLYETHYLENE GLYCOL)



L48 282 S L46 NOT PY>1999  
L49 930 S L43/AB  
L50 12 S L49 AND L48  
L51 11 S L50 NOT PY>1998

=> d ibib 6-10

L51 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1994029370 PCTFULL ED 20020513  
TITLE (ENGLISH): FACTOR IX - POLYMERIC CONJUGATES  
TITLE (FRENCH): CONJUGUES POLYMERES MODIFIANT L'ACTIVITE DU FACTEUR IX  
INVENTOR(S): HALLAHAN, Terrence, W.;  
GILBERT, Carl, W.  
PATENT ASSIGNEE(S): ENZON, INC.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9429370	A1	19941222

DESIGNATED STATES

W: AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT  
RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC  
NL PT SE

APPLICATION INFO.: WO 1994-US6388 A 19940607  
PRIORITY INFO.: US 1993-8/073,531 19930608

L51 ANSWER 7 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1994022429 PCTFULL ED 20020513  
TITLE (ENGLISH): SOLID-TUMOR TREATMENT METHOD  
TITLE (FRENCH): PROCEDE DE TRAITEMENT D'UNE TUMEUR SOLIDE  
INVENTOR(S): ALLEN, Theresa, M.;  
MARTIN, Francis, J.;  
WOODLE, Martin, C.;  
ZALIPSKY, Samuel

PATENT ASSIGNEE(S): LIPOSOME TECHNOLOGY, INC.;  
ALLEN, Theresa, M.;  
MARTIN, Francis, J.;  
WOODLE, Martin, C.;  
ZALIPSKY, Samuel

LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9422429	A1	19941013

DESIGNATED STATES

W: AU CA JP US AT BE CH DE DK ES FR GB GR IE IT LU MC NL  
PT SE

APPLICATION INFO.: WO 1994-US3457 A 19940330  
PRIORITY INFO.: US 1993-8/040,544 19930331

L51 ANSWER 8 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1994015625 PCTFULL ED 20020513  
TITLE (ENGLISH): FACTOR VIII - POLYMERIC CONJUGATES  
TITLE (FRENCH): CONJUGUES DE POLYMERES ET DE FACTEUR VIII  
INVENTOR(S): HALLAHAN, Terrence, W.;  
GILBERT, Carl, W.

PATENT ASSIGNEE(S): ENZON, INC.

LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9415625	A1	19940721

## DESIGNATED STATES

W:

AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT  
RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC  
NL PT SE

APPLICATION INFO.:

WO 1994-US552 A 19940113

PRIORITY INFO.:

US 1993-8/003,985 19930115

L51 ANSWER 9 OF 11

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

1993000109 PCTFULL ED 20020513

TITLE (ENGLISH):

METHOD OF STIMULATING IMMUNE RESPONSE USING GROWTH HORMONE

TITLE (FRENCH):

PROCEDE DE STIMULATION DE LA REPOSE IMMUNITAIRE A L'AIDE D'HORMONE DE CROISSANCE

INVENTOR(S):

CARLSSON, Lena, Mariana, Susann;

CLARK, Ross, G.;

CRONIN, Michael, J.;

JARDIEU, Paula, M.

PATENT ASSIGNEE(S):

GENENTECH, INC.

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9300109	A1	19930107

## DESIGNATED STATES

W:

AU CA JP AT BE CH DE DK ES FR GB GR IT LU MC NL SE

APPLICATION INFO.:

WO 1992-US4489 A 19920529

PRIORITY INFO.:

US 1991-723,359 19910628

L51 ANSWER 10 OF 11

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

1990004606 PCTFULL ED 20020513

TITLE (ENGLISH):

A PROCESS FOR FRACTIONATING POLYETHYLENE GLYCOL (PEG)-PROTEIN ADDUCTS AND AN ADDUCT OF PEG AND GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR

TITLE (FRENCH):

PROCEDE DE FRACTIONNEMENT DE PRODUITS D'ADDITION DE PROTEINE-POLYETHYLENE GLYCOL (PEG) AINSI QU'UN PRODUIT D'ADDITION DE PEG ET UNFACTEUR DE STIMULATION DE COLONIES DE GRANULOCYTES-MACROPHAGES

INVENTOR(S):

FISHER, Derek;

FRANCIS, Gillian, Elizabeth;

DELGADO, Cristina

PATENT ASSIGNEE(S):

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE;

FISHER, Derek;

FRANCIS, Gillian, Elizabeth;

DELGADO, Cristina

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9004606	A1	19900503

## DESIGNATED STATES

W:

AT BE CH DE FR GB IT JP LU NL SE US

APPLICATION INFO.:

WO 1989-GB1261 A 19891020

PRIORITY INFO.:

GB 1988-8824591.5 19881020

=&gt; d kwic 7

L51 ANSWER 7 OF 11

PCTFULL COPYRIGHT 2005 Univentio on STN

ABEN . . . composition has sizes predominantly in the range 0.05 to 0.12 microns,  
includes doxorubicin in entrapped form, and contains, on the PEG free ends, a monoclonal antibody specific against highly proliferative cells in a lung squamous cell

carcinoma.

ABFR . . . fois le temps de circulation dans le sang desdits liposomes par rapport a celui de liposomes depourvus de cette couche PEG. Des anticorps ou fragments d'anticorps (16), efficaces pour se lier specifiquement aux antigenes associes a la tumeur, presents sur le . . . entre 0,05 et 0,12 microns, renferme de la doxorubicine sous forme piegee, et contient, sur les extremités libres des chaines PEG, un anticorps monoclonal specifiquement dirige contre des cellules fortement proliferatives d'un epithelioma epidermoide bronchique.

DETD . . . accompanying figures and examples,  
Brief Description of the Figures  
Fig\* 1 illustrates a portion of a liposome in the liposome ocomposition of the invention, having antibodies or antibody fragments attached to the free ends of polyethylene glycol (PEG) chains carried on the liposome;  
Fig 2 shows steps in forming a PE derivatized by a PEG spacer chain having a maleimide group at its free end;  
Fig 3 illustrates the preparation of a biotinylated PE-PEG for use in preparing liposomes with PEG-bound biotin;  
Fig. 4 shows coupling of an antibody to PE derivatized with a PEG chain having a hydrazide moiety at its free end;  
Fig, 5 shows the coupling of an antibody to PE derivatized by a PEG chain having a reactive maleimide group at its free end;  
Fig\* 6 shows the coupling of an antibody to a liposome-attached PEG having a hydrazide group at its free end;  
Fig\* 7 is a plot of drug residence time in the blood, expressed in terms of percent injected dose, as a function of hours after IV injection in rats, for liposomes containing <sup>67</sup>Gallium and a bound antibody IgG (9) or liposomes with no bound antibody (A);  
Fig o 8 shows <sup>125</sup>dUrd uptake in normal and tumor-bearing DBA/2 mice (3/group) 45 days after i.v. injection of 2 x 10<sup>5</sup>.

This embodiment allows the antibody in the polymer layer to be positioned at a selected depth in the layer to increase or decrease the extent to which the antibody is buried in the polymer layer.. For example, if the antibody is a xenogeneic antibody which elicits an immunogenic-response the antibody is preferably buried to hide immunogenic sites while retaining the antigen recognition region accessible for binding to a target site. If the antibody is nonimmunogenic, the antibody can be localized on the outer surface coating of polyethylene glycol chains'. Functionalization of PEG chains for this purpose, referred to herein as a spacer chain, for attachment of an antibody is described below.

In another embodiment the antibody is a biotinylated antibody attached to the distal ends of liposome-attached polymer ends via a biotin-

streptavidin (or biotin-avidin) linkage, In one embodiment, shown in Fig. 3, a DSPE-PEG-NH<sub>2</sub> is converted to DSPE-PEG-biotin. To the biotin moiety on the PEG free ends are bound avidin or streptavidin molecules. Each avidin molecule contains four high-affinity biotin binding sites and to one or more of these sites is attached the liposome bound biotin. To one or more of the free-remaining sites can be bound a biotinylated antibody which is derivatized by a biotin molecule.

The liposomes are then incubated with avidin and biotinylated antibody. Alternatively, a DSPE derivatized with a PEG chain having a hydrazide group at the chain's free end may be synthesized, as illustrated in Fig. 4\*. Here, a hydroxy acid derivative (IX) is prepared from PEG using ethyl isocyanatoacetate for partial introduction of a urethane-linked glycine residue.

30-75 percent vesicle-forming lipids, 25-40 percent cholesterol, 1-20 percent polymer-derivatized lipid, and 0-10 mole percent of the lipid derivative employed for antibody coupling, one exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), DSPE-PEG at a molar ratio of 2:1:0.1. The composition also includes 0.05 mole percent phosphatidylethanolamine derivatized with biotin (biotin-PE). Another exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), and DSPE-PEG at a molar ratio of 2:1:0. The composition also includes 1 mole percent DSPE-PEG derivatized with hydrazide (DSPE-PEG-Hz).

Alternatively, an antibody-lipid derivative may be first formed and then incorporated into a liposome. As an example, an antibody is coupled to the maleimide group of a free DSPE-PEG molecule. The antibody-coupled DSPE-PEG molecule is then employed to form vesicles.

Alternatively, the polymer end-functionalized group is a hydrazide group (see Figure 4 discussed above). Conveniently, the hydrazide can be coupled to the antibody through the carbohydrate moieties present in the antibody, as detailed in Figure 6 and Example 1.VIII. Briefly, antibody hydroxyl groups are oxidized to aldehydes by mild periodate oxidation. The oxidized protein is then added to liposomes containing DSPE-PEG-Hz and incubated overnight. Unbound antibodies are then separated from antibody-liposomes by gel filtration.

#### Ive Utility

According to an important aspect of the invention, it has been found that antibodies can be attached to the PEG chain free ends without a significant loss in the blood circulation lifetime of the liposomes. This allows the antibody-coated liposomes to circulate for the time necessary to reach remote tumor sites and to localize at the

sites through antibody-antigen specific interactions. As a result, a significant therapeutic enhancement in tumor treatment over long-circulating liposomes in the absence of surface attached antibodies is possible.

A, Therapeutic Efficacy of Antibody-liposome Composition in vivo  
Experiments were performed to investigate the half-life in the bloodstream and the tissue biodistribution of the antibody]liposome composition. For these experiments liposomes containing PEG end-functionalized with a hydrazide group covalently linked to sheep IgG were prepared as described in Example 1.VIII.

The tissue biodistribution of liposomes containing <sup>125</sup>I-tyraminylinulin with and without covalently attached IgG antibodies is shown in Table I (Example 2(I)). It can be seen that the tissue biodistribution of liposomes containing antibody covalently attached to the end of a PEG chain by a hydrazide group is very similar to those of liposomes containing nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood, liver, spleen, lung,, heart and carcass.

Other experiments to determine the blood circulation times of antibody-liposomes were performed using liposomes containing surface-bound avidin and biotinylated antibodies. Liposomes with surface-bound antibodies possessed long circulation times in the bloodstream similar to that of liposomes containing PEG derivatized lipids but lacking the surface-bound antibodies.

Twenty-four hours post-injection 34.7  $\pm$  6.7% of .WO 94/22429 PCTIUS94/03457

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mAb liposomes were in the blood. This level is comparable to that of liposomes containing PEG, but lacking the antibody (37.5  $\pm$  9.7% at 24 hours).

The results obtained indicate that liposomes containing entrapped doxorubicin, lipids derivatized with PEG, such as PEG]DSPE, and containing an antibody on the liposomes' outer surface (mAb-liposomal DOX) are valuable for increasing the therapeutic effectiveness of doxorubicin administration to a site in a subject.

compound,  
multivalent species capable of binding multiple antibodies may be administered between about 24 to 48 hours after administration of the biotinylated antibodies to accelerate clearance of the antibodies from the bloodstream. These multivalent species may be empty liposomes having surface-bound avidin, but not containing the liposome-entrapped compound, The empty. . .

These multivalent species serve to chase nonspecifically-bound biotinylated antibodies from

sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as, avidin, and the PEG layer on the liposome surface are administered.

#### Example 1

##### Preparation of DSPE-PEG-Maleimide and Antibody Coupling to DSPE-PEG-Maleimide

To Preparation of the Mono 2-nitrobenzene-sulfonamide of PEG bis(amine) (Compound II)  
A mixture of 1.7 g (0.5 mmole) of commercially available polyethylene glycol bis(amine) and 104 mg (0.55 mmole) of 2-nitrobenzene. . .

#### VII. Antibody Coupling to the Maleimide Group of PEG

Coupling reactions were performed by adding antibody solution to the liposomes (final protein concentration = 0.5 mg/ml) in phosphate buffered saline and incubating the suspension overnight at ambient temperature with. . .

#### VIII. Antibody Coupling to the Hydrazide Group of PEG

A 10 mg/ml solution of IgG was prepared in 100 mM sodium acetate, 70 mM NaCl pH 5 For 1 ml of protein. . . of 0.2 M sodium periodate was added. oxidation proceeded for 1 hour at room temperature. The periodate-treated protein was added to liposomes containing DSPE-PEG hydrazide and incubated overnight at 40C.

Liposomes were separated from free protein by chromatography on Sepharose CL-4B in TES-buffered saline, pH 7.4\*

#### Example 2

##### Biodistribution of Antibody-Liposomes

The biodistribution and blood circulation lifetime of liposomes containing surface-bound antibodies was compared to that of liposomes lacking surface-bound antibodies. The antibody-liposomes were composed of HSPC:CH:PEG hydrazide, at a 2:1:0.1 molar ratio, and sheep IgG covalently linked to PEG chain. Liposomes lacking surface-bound antigens were liposomes composed of HSPC:CH:PEG at a 2:1:0.1 molar ratio and liposomes, composed of HSPC:CH:PEG hydrazide. The average diameter of the liposomes was between 110 and 120 nanometers. For biodistribution studies the liposomes contained <sup>125</sup>I-tyraminylinulin in liposome-entrapped form (Example 2(I)). For blood circulation lifetime studies the liposomes contained <sup>67</sup>Ga in liposome-entrapped form, The antibody-liposomes were prepared as described in Example 1.VIII.

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As shown in Table 1 the biodistribution of liposomes containing antibody covalently attached to the end of a PEG chain by a hydrazide group are very similar to those of liposomes containing 30 nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood,

liver, spleen, lung, heart and carcass.

of

either 0.2 ml phosphate-buffered saline (PBS) (untreated controls) or with 6 mg/kg of either free DOX, 6 mg/kg of DOX entrapped in HSPC:CH:PEG-DSPE liposomes (liposomal DOX), 6 mg/kg of DOX entrapped in HSPC:CH:PEG-DSPE liposomes containing attached antibody 174H.64 (mAb-liposomal DOX) or mAb-liposomes (11-39 Ag mAb) lacking DOX, all in 0\*2 ml of sterile saline.

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L51 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN Conjugates containing a substance with coagulant activity, such as recombinant Factor IX, non-antigenic polymers, such as poly(ethylene glycol), are disclosed. Also disclosed are methods of forming the novel conjugates of this invention.  
ABFR . . . substance presentant une activite coagulante, tels que le facteur IX de recombinaison, et des polymeres non antigeniques tels que du poly(ethylene glycol); et procedes de preparation de ces nouveaux conjugues.  
DETD . . . to a final concentration of 10 .mM and was allowed to sit on ice for 5 minutes, Excess periodate and sucrose were removed by desalting on a PD-10 column as described above. A 100 fold excess PEG-Hydrazide was added, and the reaction proceeded. . . was added to a final concentration of 5 mM and the mixture was kept refrigerated overnight, Excess PEG and NaCNBH4 were removed by GPC-HPLC using a Showdex column equilibrated with 0,1 M sodium phosphate pH 7,5, SDS-PAGE of the purified material revealed a . . . 100 mM NaCl with 10 mg/ml glycine, The sample was aliquoted -and stored at either 40C, -700C or lyophilized, SDS-PAGE revealed an increased and broad molecular weight distribution but no sign of contaminating native protein, Specific activities were \*determined in the presence of Factor IX def. . .

SAMPLE SPECIFIC ACTIVITY (U/mg)

Native Factor IX 47  
PEG-F,IX (40C) 128  
PEG-F\*IX (-700C) 146  
PEG-F,IX (Lyoph) 115

The various embodiments of the present invention,, therefore, provide conjugates which retain significant levels of Factor IX activity while having less of a tendency to cause the formation of inhibitor antibodies.

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L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1986004145 PCTFULL ED 20020507  
TITLE (ENGLISH): PROTEIN MODIFICATION WITH PEG  
TITLE (FRENCH): MODIFICATION DE PROTEINES AVEC PEG  
INVENTOR(S): TOMASI, Thomas, B.;  
ANDERSON, William, L.  
PATENT ASSIGNEE(S): UNIVERSITY OF NEW MEXICO

LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
DESIGNATED STATES	WO 8604145	A1	19860717
W:	DE GB JP		
APPLICATION INFO.:	WO 1985-US2572	A	19851231
PRIORITY INFO.:	US 1984-687,811		19841231

=> d kwic 11

L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN PEG-modified protein molecules characterized by reduced immunogenicity are prepared by covalent modification of the protein with PEG employing an active ester intermediate. Antibodies so modified exhibit decreased binding capacity for Fc cell surface receptors, are non-toxic and. . . .  
ABFR Des molecules de proteines modifiees par PEG (polyethylene glycol) caracterisees par une immunogenicite reduite sont preparees par modification covalente de la proteine avec PEG utilisant un intermediaire d'ester actif. Des anticorps ainsi modifies presentent une capacite de liaison diminuee pour des recepteurs en surface. . . .  
DETD PROTEIN MODIFICATION WITH PEG  
F i eld--of  
Diagnostic and therapeutic procedures of the type dependent upon immunoreaction of antibody with a target tissue are frequently hampered by both the immunogenicity of the reagent in clinical applications and binding to cell surface Fc receptors, Immune response to antibodies and other foreign proteins, characterized by both allergic phenomena and inactivation of the protein, must be countered by treatment of the protein to obviate stimulation of the host immune system, while retaining desirable protein biologic activity, In addition, it is desirable to increase antibody specificity by reduction or elimination of Fc binding to cell surface receptors.  
result was obtained in a related study J.\_\_\_\_T 1 nnol . hiad mm --l-le-t s., 327 (1983), wherein it was concluded that PEG-modification of Ig mediated with cyanuric chloride destroyed antibody activity.  
comprises a polyethylene glycol-protein derivative, and a method for preparing the derivative in excellent yields comprising covalently modifying the protein with polyethylene glycol (PEG) employing an active ester intermediate. Derivatized antibodies are characterized by retained antigen binding activity, low binding capacity for cell surface Fc recep-torsr reduced in,munogenicity, good storage stability, and non-toxicityf'and are. . . . such as tumor imaging, chemotherapy, radiotherapy, and iiiurnunohistochemical procedures. It is contemplated that a broad range of diagnostic and therapeutic proteinsr including monoclonal antibodies and enzymes, is modifiable by the process of the invention to provide



modified proteins having reduced immunogenicity and low non-specific biological.

Different symbols depict experiments performed on different days with different samples of PEG-modified antibody

An affinity purified rabbit anti-mouse immunoglobulin reagent was modified with FITC to an F/P ratio of 3.7. A fraction of TPIPTOM Qz TRE

According to the invention, immunogenicity of foreign protein, especially antibody, is reduced or eliminated by covalent

modification of the protein with polyethylene glycol (PEG), employing a PEG active ester intermediate. In contrast to known

prior art modifications, PEG modification of antibodies according

to the process of the invention provides a derivative which retains avidity for antigen, while exhibiting reduced immunogenicity. A particular advantage is reduction in non-specific binding which occurs which

is believed to be attributable to inactivation of the Fc portion of the antibody molecule. The process thus substantially eliminates binding of the antibody to cell surface Fc receptors and promotes

antibody concentration targeted tissue in applications such as tumor imaging and immunohistochemical techniques.

Particular PEG polymers useful in the process of the invention comprise substituted or unsubstituted PEG polymers having molecular weights of from about 1000 to 5000 which are themselves poor immunogens, and which can be coupled to protein using. . . biologically active and substantially non-toxic and non-immunogenic. monomethoxypolyethylene glycol (mPEG) satisfies these criteria, and is an especially suitable modifier, particularly for antibody. Covalent mPEG modification of antibody molecule,

using the present active ester approach is accomplished with full retention of binding activity, and yields very predictable and reproducible modifications.

While the

process is particularly useful in reducing the immunogenicity of heterologous species proteins, the process is also applicable to homologous species proteins. Antibodies are proteins of particular interest, as by the process of the invention, the specificity and avidity of the antibody molecules is retained, while non-specific binding of antibody molecules to cellular Fc receptor and rapid clearance of the antibody from the circulation

is obviated. Drugs, toxins, fluorescents, radionuclides, or other active moieties may readily be attached to the modified

antibody molecule via the PEG substituent according to principles

understood by those skilled in the art for delivery to selected tissue, especially to tumor tissue for diagnosis or therapy, owing to the decreased non-specific activity of complexes comprising active moieties conjugated with PEG-modified antibody or other

protein, premature dissociation of the complex is avoided and highly selective delivery is achieved.

brief, antisera

was applied to the affinity column and the column was washed

with 0.5 U sodium thiocyanate and the resulting antibody was simultaneously desalted and concentrated using a Micro Pro di Con apparatus, (Bio Molecular Dynamics Beaverton OR). The purified antibody was stored sterile at 4 degrees, .-e.asjurement.o.f Anti-Conalbumin Activity

Antigen binding activity of the affinity purified and chemical-ly modified antibodies was determined by evaluating their ability to competitively inhibit the binding of a rabbit anti-conalbumin-alkaline phosphatase conjugate to conalbumin-coated micAroelisa plates (Vanguard, Neptune, NJ). The enzyme linked antibody for this assay was prepared by a modification of the method described by Avermeas (Immunol. Chem. ]: 43j, 1969) and to assure. . . conalbumin to 10 ug/ml in 0.05 U NaHCO<sub>3</sub> r pH 9.6 and incubating for 18 hours at room temperature, Equal volumes of antibody and enzyme conjugate, at the proper dilution, were then incubated in the antigen coated plates with Characteriza-tio.ja-af. Modified.-Antibod

Three different measurements were used to characterize the modified antibody. Protein concentration was determined both by optical density measurements at 280 nm, . assuming an E % 280nm = 14 Qlatho.ds.-Immuna.l. Immunochem.2: 343,. . . , 1 948) Protein amino groups were determined by TNBS titrations as described by Habeeb (Anal. Chem. 38: 1700, 1966) The extent of PEG modification was also evaluated by measuring an increase in protein size. For this measurement protein size was evaluated using a 0.6% discontinuous. . .

Determination of immunogenicity of rabbit antibody and its PEG-modified derivatives were determined by measuring the antibody response of Swiss mice to an intraperitoneal injection of 50 µg of the antigen (rabbit antibody) in PBS. The mouse antibody response was determined using a two step enzyme linked assay, In brief several two-fold dilutions of mouse sera were incubated on a rabbit. . .

The effect of mPEG modifications, using cyanuric chloride and active ester coupling procedures on antibody activity is reported in Table I and II. It is evident from these results that even at low modifications there is a significant decrease in antibody binding activity with cyanuric chloride.

Experiments varying the rate and form of activated PEG along with experiments varying the reaction time and temperature did not significantly improve the recovery of active antibody. In contrast the use of active ester to modify antibody with PEG results in no detectable loss in antibody titer or antibody activity.

TABLE I  
Antigen binding activity of -Rat' albumin  
Modified with ag using -the, ]Xanthiric Chloride. Procedure  
% Lysine

Modification	mg Antibody/mg Protein	% Loss of Ab Activity
1*00	0	
0050	50	
0*15	35	
0*06	94	

TABLE II  
Activity of Rabbit

Anti-CQ Modified. with  
ha, ra=9 ;Ler- of

% Lysine

Modification mg Antibody/mg Protein % Loss of Ab Activity

1 0 0 0

1\*0 0

1\*0 0

1\*0 0

100 0

1\*0 0

at ion, o

EXAMPTA.-I-n-, Effectiy. ansa Qf

I.--w th mPZQ. a lo-the-,

To verify that antibody was significantly modified by  
this procedure, all mPEG-modified antibody preparations were  
analyzed by SDS gel electrophoresis. An example of one series  
of derivatives is shown in FIG. 1e Results from this experiment

clearly show that most or all molecules in the population are  
modified and that the apparent molecular weight increases  
greatly

following the modification. II-. should be noted however that  
the -modified antibodies tested are a distribution of  
molecules

each containing different number of PEG molecules per  
antibody.

B. The hyperresponsiveness induced by some of the mPEG-  
modified rabbit antibodies in A, gap-ra, was investigated by  
evaluating the adjuvant properties of PEG. Swiss mice were  
immunized with 50 mg of rabbit immunoglobulin in the presence  
of varying PEG concentrations up to 1 mg/ml PEG and  
the antibody  
response determined fifteen days later. In this experiment  
the PEG was not covalently attached to the rabbit protein.

appear to have

an upper limit to the cellular fluorescence intensity whereas  
cells detected by the reagent that was not mPEG-modified show  
an increased fluorescence intensity (FIG. 7B)

It was demonstrated that the mPEG-modified reagent  
binds to cell surface immunoglobulin whereas the non mPEG-modified  
reagent exhibits. . . immunoglobulin was used

to competitively inhibit the binding of both reagents to mouse  
splenocytes. The results of this experiment, shown in FIG. 8,

clearly demonstrate that the binding of the classical  
fluoresce-

inated reagent (not mPEG-modified) could not be completely, inhibited  
by antigen whereas binding of. . .

PEG-modified antibodies according to the invention  
exhibit

markedly reduced immunogenicity, low specific binding capacity  
for cell surface Fc receptors, and retention of antigen-binding  
activity. mPEG modification of antibodies also essentially  
eliminates Fc receptor binding. Covalent modification of more  
than 15% of amino groups of rabbit anti-conalbumin antibody  
with mPEG completely prevented immune complexes prepared with  
this antibody from binding to the Fc receptor on the murine  
macrophage cell line P388, D1. Similar sensitivities are observed  
for mPEG-modified fluorescein labelled antibodies since mPEG  
modification does not quench fluorescein fluorescence. A fluorescein  
WO 86/04145 PCT/US85/02572

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY () ETHYLENE () GLYCOL  
L5 52 S METHOXYPOLY () ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY () ETHYLENE () GLYCOL  
L22 144 S METHOXYPOLY () ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999  
L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
L35 5321 S POLY () ETHYLENE () GLYCOL  
L36 76 S METHOXYPOLY () ETHYLENE GLYCOL  
L37 80487 S ANTIBOD?  
L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40  
L43 38102 S L34 OR L35 OR L36  
L44 3934 S L43 (S) L37  
L45 1413 S L44 AND L40  
L46 1018 S L44 (P) L40  
L47 3 S ANTI () (POLYETHYLENE GLYCOL)  
L48 282 S L46 NOT PY>1999  
L49 930 S L43/AB  
L50 12 S L49 AND L48  
L51 11 S L50 NOT PY>1998

=> file dissab  
COST IN U.S. DOLLARS

SINCE FILE

TOTAL

FULL ESTIMATED COST	ENTRY 56.84	SESSION 135.66
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-1.46

FILE 'DISSABS' ENTERED AT 08:36:44 ON 23 AUG 2005  
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```
=> s anti-peg
      25082 ANTI
        9 ANTIS
      25087 ANTI
        (ANTI OR ANTIS)
      1251 PEG
      154 PEGS
      1334 PEG
        (PEG OR PEGS)
L52      0 ANTI-PEG
        (ANTI(W) PEG)

=> s anti () (polyethylene glycol)
      25082 ANTI
        9 ANTIS
      25087 ANTI
        (ANTI OR ANTIS)
      3287 POLYETHYLENE
      146 POLYETHYLENES
      3344 POLYETHYLENE
        (POLYETHYLENE OR POLYETHYLENES)
      2420 GLYCOL
      177 GLYCOLS
      2537 GLYCOL
        (GLYCOL OR GLYCOLS)
      930 POLYETHYLENE GLYCOL
        (POLYETHYLENE(W)GLYCOL)
L53      0 ANTI (W) (POLYETHYLENE GLYCOL)
```

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

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E "PEG"/CN 25
L1      1 S E3
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L6      10866 S L5 OR L4 OR L3
L7      694206 S ANTIBOD?
```

L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
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L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
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L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
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L32 3 S L31 NOT PY>1999  
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L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40  
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L45 1413 S L44 AND L40  
L46 1018 S L44 (P) L40  
L47 3 S ANTI () (POLYETHYLENE GLYCOL)  
L48 282 S L46 NOT PY>1999  
L49 930 S L43/AB  
L50 12 S L49 AND L48  
L51 11 S L50 NOT PY>1998

FILE 'DISSABS' ENTERED AT 08:36:44 ON 23 AUG 2005

L52 0 S ANTI-PEG  
L53 0 S ANTI () (POLYETHYLENE GLYCOL)

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
FULL ESTIMATED COST	ENTRY	SESSION
	0.41	136.07
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
CA SUBSCRIBER PRICE	ENTRY	SESSION
	0.00	-1.46

STN INTERNATIONAL LOGOFF AT 08:37:23 ON 23 AUG 2005

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

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NEWS 3 DEC 05 CASREACT(R) - Over 10 million reactions available

NEWS 4 DEC 14 2006 MeSH terms loaded in MEDLINE/LMEDLINE

NEWS 5 DEC 14 2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER

NEWS 6 DEC 14 CA/CAPLUS to be enhanced with updated IPC codes

NEWS 7 DEC 21 IPC search and display fields enhanced in CA/CAPLUS with the  
IPC reform

NEWS 8 DEC 23 New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/  
USPAT2

NEWS 9 JAN 13 IPC 8 searching in IFIPAT, IFIUIDB, and IFICDB

NEWS 10 JAN 13 New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to  
INPADOC

NEWS 11 JAN 17 Pre-1988 INPI data added to MARPAT

NEWS 12 JAN 17 IPC 8 in the WPI family of databases including WPIFV

NEWS 13 JAN 30 Saved answer limit increased

NEWS 14 JAN 31 Monthly current-awareness alert (SDI) frequency  
added to TULSA

NEWS 15 FEB 21 STN AnaVist, Version 1.1, lets you share your STN AnaVist  
visualization results

NEWS 16 FEB 22 Status of current WO (PCT) information on STN

NEWS 17 FEB 22 The IPC thesaurus added to additional patent databases on STN

NEWS 18 FEB 22 Updates in EPFULL; IPC 8 enhancements added

NEWS 19 FEB 27 New STN AnaVist pricing effective March 1, 2006

NEWS 20 FEB 28 MEDLINE/LMEDLINE reload improves functionality

NEWS 21 FEB 28 TOXCENTER reloaded with enhancements

NEWS 22 FEB 28 REGISTRY/ZREGISTRY enhanced with more experimental spectral  
property data

NEWS 23 MAR 01 INSPEC reloaded and enhanced

NEWS 24 MAR 03 Updates in PATDPA; addition of IPC 8 data without attributes

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